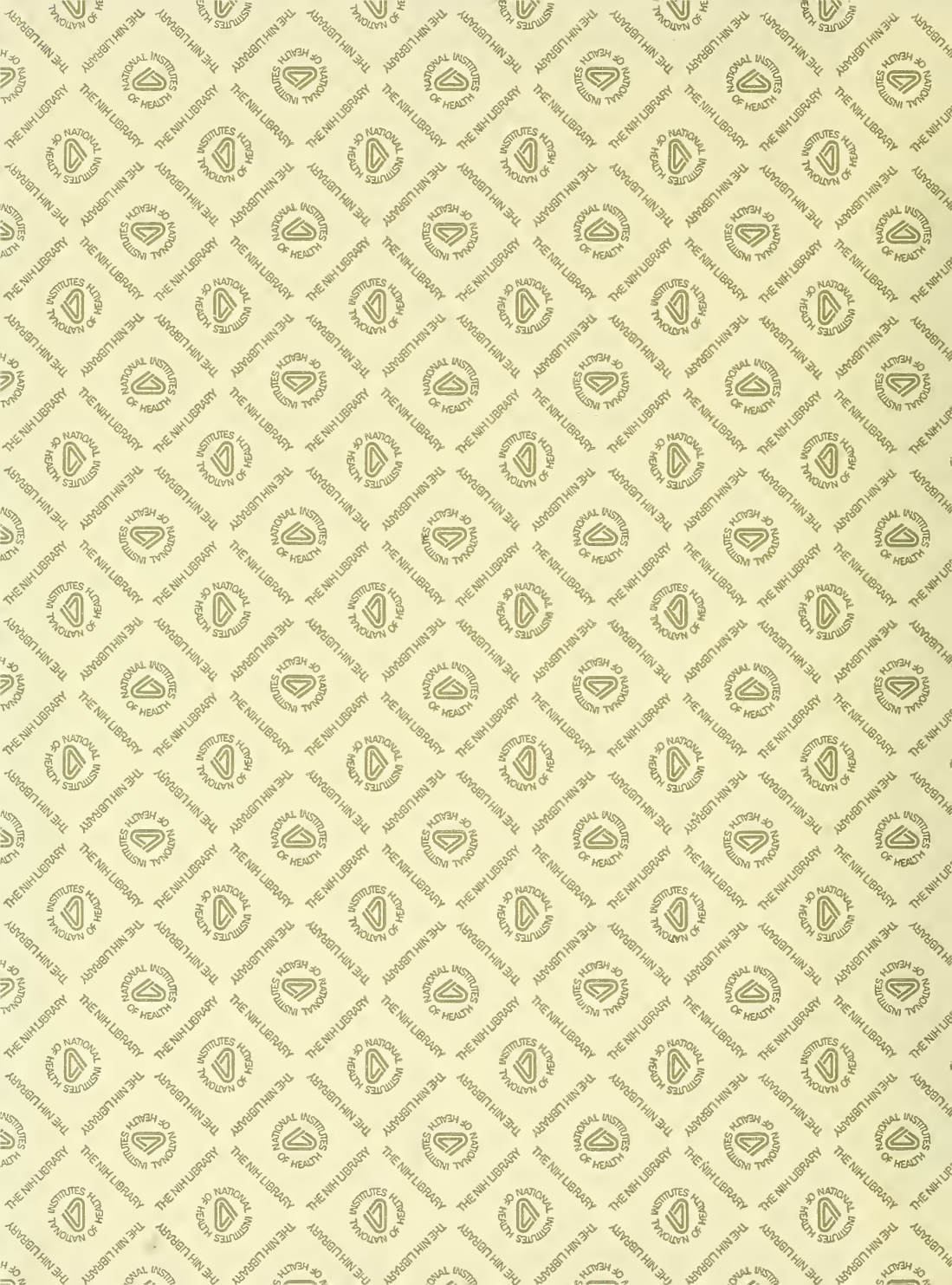
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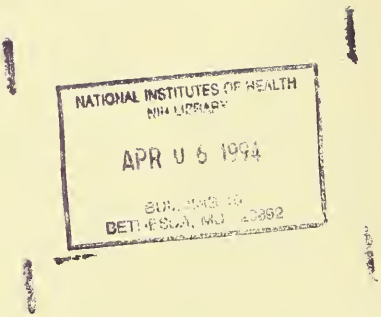

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00001-09 BPGS

PERIOD COVERED

October 1 1992 to September 30 1993

TITLE OF PROJECT

Control of Behavior by Drug Injection

PRINCIPAL INVESTIGATOR

P.I.	CA Sannerud	Senior Staff Fellow	Preclinical Pharmacology Laboratory
	SR Goldberg	Chief	Preclinical Pharmacology Laboratory
	CW Schindler	Research Psychologist	Preclinical Pharmacology Laboratory
	SL Serdikoff	IRTA	Preclinical Pharmacology Laboratory
	JA Prada	Research Psychologist	Preclinical Pharmacology Laboratory

COOPERATING UNITS

LAB/BRANCH

Preclinical Pharmacology Laboratory

SECTION

Behavioral Pharmacology

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
4.3	2	2.3

CHECK APPROPRIATE BOXES

☐ (A) Human ☐ (b) Human Tissue ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

Drugs serve as positive reinforcers to maintain and strengthen behavior leading to their administration and can control behavior through their ability to function as discriminative stimuli. In many situations, drugs of abuse function through pharmacological and behavioral mechanisms to persistently sustain long sequences of drug seeking behavior that are very resistant to extinction. These long sequences of drug-seeking behavior can be analyzed using schedule-controlled performances in the same way as operant behavior maintained by other events such as food or shock. Using a variety of intravenous self-administration procedures in rats and primates, ongoing experiments are being conducted to evaluate behavior maintained by drugs and the ability of pharmacological treatments, (e.g., antagonist administration or the development of dependence) and/or behavioral manipulations to modify drug self-administration behavior and/or food-maintained behavior. These studies will compare responding maintained under fixed-ratio, fixed interval and complex second-order schedules, by various drugs including cocaine, nicotine and other psychomotor stimulants, benzodiazepines and other sedative/anxiolytics, and morphine and other opioids. For example, since recent studies suggest a serotonergic mechanism underlying psychomotor stimulant action, an ongoing study is assessing the effects of sertraline, a selective serotonergic uptake inhibitor that is effective as an antidepressant, on the reinforcing effects of i.v. nicotine in squirrel monkeys. In addition to differences in the pharmacological efficacy of drugs to control or modify behavior, it is clear that behavioral and environmental factors play an important role in the control that even highly efficacious drugs exert on behavior. The focus of experiments in the rhesus self-administration lab are to study the pharmacological, behavioral, and environmental variables involved in initiating and maintaining drug self-administration. Since the ability of psychoactive drugs to maintain self-injection behavior will be modified by a number of environmental and behavioral factors, additional studies will be initiated to evaluate the development of tolerance to the reinforcing effects of psychoactive drugs and how the development of tolerance can be attenuated by environmental conditions. Additionally, studies of "drug-seeking behavior" will be initiated using a choice procedure that manipulates the delay of reinforcement and magnitude of the drug reinforcer (i.e., dose).

Goldberg DM, Goldberg SR. Experimental analysis of the reinforcing effects of nicotine. In: Cohen-Yanez J, Arnezcua-Gastelum JL, Villarreal J, Zavala LS, Drug dependence from the molecular to the social level. Amsterdam: Elsevier, 1992; 311-320.

Gannerud CA, Ator NA, Griffiths RR. Behavioral pharmacology of abecarnil in baboons. In: Stephens DN ed. Preclinical Pharmacology of Abecarnil. Berlin: Springer-Verlag, in press.

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Gannerud CA, Ator NA, Griffiths RR. Behavioral pharmacology of tandospirone in baboons: Chronic administration and withdrawal, self-injection and drug discrimination. Drug Alcohol Dependence 1993; 32: 195-208.

Gasar S, Goldberg SR, Winger G, Nickel B, Schultz G. Preclinical evaluation of l-deprenyl: lack of amphetamine-like abuse potential. In: Szelenyi I, ed. Inhibitors of monamine oxidase B. Birkhauser, 1993; 215-233.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00002-08 CDM

PERIOD COVERED

October 1 1992 to September 30 1993

TITLE OF PROJECT

Validity Studies of Commercial Drugs Screening Assays

PRINCIPAL INVESTIGATOR

P.I.	EJ Cone	Chief	Clinical Pharmacology Branch
	WD Darwin	Chemist	Clinical Pharmacology Branch
	A Jenkins	Staff Fellow	Clinical Pharmacology Branch
	D Yousefnejad	Chemist	Clinical Pharmacology Branch

COOPERATING UNITS

LAB/BRANCH

Clinical Pharmacology Branch

SECTION

Chemistry

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
0.6	0.2	0.4

CHECK APPROPRIATE BOXES

☒ (A) Human ☐ (b) Human Tissue ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

Commercial assays for the detection of drugs of abuse in urine changeperiodically and must be reevaluated for performance. Studiesare designed to test the validity of new assays on clinical specimens obtained from drug users under controlled conditions.

Healthy male volunteers with a history of chemical substance abuse participate in these studies. Informed consent is obtained and all procedures are approved by the hospital Institutional Review Board. Commercial assays for detection of drugs of abuse in urine are tested for validity with specimens collected under controlled dosing conditions.A variety of drugs of abuse are studied at various dose levels. The results of the assays are compared to GC/MS analyses.

These studies test the validity of commercial assays on clinical samples instead of "spiked" samples and provide unique and valuable information to the military and industry concerning their time course of detection, specificity and accuracy.

one, E.J., Dickerson, S.L., Paul, B.D. and Mitchell, J.M., Forensic Drug Testing For Opiates V. Urine Testing or Heroin, Morphine And Codeine With Commercial Opiate Immunoassays. J. Anal. Toxicol., 17: 156-164, 993.

enkins, A.J., Mills, L.C., Darwin, W.D., Huestis, M. A. and Cone, E. J. Validity Testing Of The EZ-Screen: annabinoid Test. J. Anal. Toxicol., In Press, 1992.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00003-08 BPGS

PERIOD COVERED

October 1 1992 to September 30 1993

TITLE OF PROJECT

Effects of Drugs on Schedule-Controlled Behavior of Experimental Animals

PRINCIPAL INVESTIGATOR

P.I.	SR Goldberg	Chief	Preclinical Pharmacology Laboratory
	CA Sannerud	Senior Staff Fellow	Preclinical Pharmacology Laboratory
	CW Schindler	Research Psychologist	Preclinical Pharmacology Laboratory
	M Gewiss	Visiting Fellow	Preclinical Pharmacology Laboratory
	S Yasar	Guest Worker	Preclinical Pharmacology Laboratory

COOPERATING UNITS

LAB/BRANCH

Preclinical Pharmacology Laboratory

SECTION

Behavioral Pharmacology

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER
4.9	3	1.9

CHECK APPROPRIATE BOXES

☐ (A) Human ☐ (b) Human Tissue ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

The behavioral pharmacological profile of a drug in a pertinent species is necessary to evaluate quantitatively how the drug functions as a reinforcer or a punisher as well as to establish its stimulus effects. Schedules of food presentation with both fixed-interval and fixed-ratio components have been used most frequently in this type of study since they generate a wide range of rates and patterns of responding within a session and provide stable, long-term baselines for chronic studies in individual animals. The present project involves the assessment of both the acute and chronic effects of a variety of drugs on schedule-controlled behavior. We have recently shown that the enhanced sensitivity observed to the behavioral effects of the opioid antagonist naltrexone is influenced by GABAergic processes, and in particular by an action at the GABA associated chloride channel. Further, this sensitivity may be associated with changes in both mu and delta opioid receptors. Genetic factors are known to influence the behavioral effects of a number of different drugs, and studies of the interactions between environmental and genetic components that potentially affect the development of behavioral tolerance and sensitivity are being initiated. Behaviorally active drugs can also serve as discriminative stimuli to guide behavioral choice. Ongoing two- and three-lever drug discrimination projects in the laboratory have helped to define and characterize the spectrum of behavioral effects produced by the drug, to compare a range of other compounds, such as cocaine, l-deprenyl, morphine, midazolam, and caffeine to characterize the relative potency and efficacy to produce drug-like effects, and to evaluate the drug's mechanisms of action at the receptor level. Since most human drug-taking behavior involves chronic long-term use of an illicit drug or non-medical abuse of a prescribed medication, the consequences of chronic administration of drugs on schedule-controlled behavior and the discriminative functions of drugs are being evaluated. Although the development of tolerance and dependence are related to pharmacological factors, tolerance can also be modified by environmental factors. For example, the interaction between drug administration and the ability to perform the task can result in differential tolerance that is a function of chronic daily dose and duration of treatment.

lumford GK, Evans SM, Kaminski BJ, Preston KL, Sannerud CA, Silverman K, Griffiths RR. Discriminative imulus and subjective effects of theobromine and caffeine in humans. Psychopharmacology; in press.

ersico AM, Schindler CW, Brannock MT, Gonzalez AM, Surratt CK, Uhl GR. Dopaminergic gene expression uring amphetamine withdrawal. Neuroreport 1993; 4: 41-44.

ersico AM, Schindler CW, O'Hara BF, Brannock, MT, Uhl GR. Brain transcription factor expression: Effects of cute and chronic amphetamine and injection stress. Mol Brain Res in press.

annerud CA, Griffiths RR. Modification of tolerance to midazolam discriminative stimulus effects: evidence ose fading. Behav Pharmacol 1993; 4: 125-134.

annerud CA, Marley RJ, Serdikoff SL, Alastra AJG, Cohen C, Goldberg SR. Tolerance to the behavioral ffects of chlordiazepoxide: Pharmacological and biochemical selectivity. J Pharmacol Exp Ther; in press.

chindler CW, Goldberg SR, Katz JL. Pharmacological specificity of enhanced sensitivity to naltrexone in rats. sychopharmacology 1993; 110: 60-68.

chindler CW, Thorndike EB, Goldberg SR. Acquisition of a nose-poke response in rats as an operant. Bul sychonomic Soc 1993; 31: 291-294.

chindler CW. Classical conditioning. In: van Haaren F, ed. Methods in behavioral pharmacology. msterdam: Elsevier, 1993: 53-79.

wedberg MDB, Shannon HE, Nickel B, Goldberg SR. D-16949 (anpirtoline): A novel serotonergic (5-HT1B) sychotherapeutic agent assessed by its discriminative effects in the rat. J Pharmacol Exp Ther 1992; 263: 015-1022.

'eiss SJ, Panlilio LV, Schindler CW. Selective associations produced solely with appetitive contingencies: he stimulus-reinforcer interaction revisited. J Exp Anal Behav 1993; 59: 309-322.

'eiss SJ, Panlilio LV, Schindler CW. Single-incentive selective associations produced solely as a function of ompound-stimulus conditioning context. J Exp Psychol: Animal Behav Processes 1993; 19: 284-294.

asar S, Schindler CW, Thorndike EB, Szelenyi I, Goldberg SR. Evaluation of the stereoisomers of deprenyl r amphetamine-like discriminative stimulus effects in rats. J Pharmacol Exp Ther 1993; 265: 1-6.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00009-07 BPGS

PERIOD COVERED

October 1 1992 to September 30 1993

TITLE OF PROJECT

Cardiovascular Changes Induced by Cocaine

PRINCIPAL INVESTIGATOR

P.I.	CW Schindler	Research Psychologist	Preclinical Pharmacology Laboratory
	SR Goldberg	Chief	Preclinical Pharmacology Laboratory
	SR Tella	Guest Worker	Preclinical Pharmacology Laboratory
	HK Erzouki	Visiting Fellow	Preclinical Pharmacology Laboratory
	E Buchert	IRTA	Preclinical Pharmacology Laboratory

COOPERATING UNITS

Dept of Pharmacology, Georgetown University

LAB/BRANCH

Preclinical Pharmacology Laboratory

SECTION

Behavioral Pharmacology

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
4.7	3.4	1.3

CHECK APPROPRIATE BOXES

☐ (A) Human ☐ (b) Human Tissue ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

Cardiovascular effects of cocaine are being extensively studied using various species of animals as model systems. For all the conscious species studied, cocaine (0.03-3.0 mg/kg, i.v.) produces a dose-dependent and prolonged increase in mean arterial blood pressure and heart rate. Studies in rats have shown that inhibition of peripheral sympathetic neuronal amine uptake mechanism by cocaine is not critical for initiating cocaine's pressor, tachycardiac and plasma catecholamine increasing effects and that central stimulation of the sympathoadrenal neural axis activity plays an important role in these effects. The peak pressor effect of cocaine is mediated by norepinephrine of sympathetic neural origin and the peak tachycardiac effect of cocaine is mediated by epinephrine of adrenal medullary origin. To investigate the role of the cocaine metabolites in cocaine toxicity, we have also investigated the hemodynamic and cardiac-electrophysiological effects of cocaine and its metabolites in anesthetized, artificially-ventilated rats during continuous i.v. infusions. At the highest dose (1.5 mg/kg/min), cocaine decreased blood pressure and heart rate, while QRS duration, an index of cocaine's local anesthetic effect, was increased. Cocaethylene, a metabolite produced following co-administration of cocaine and ethanol, had effects comparable to those of cocaine. The cocaine metabolite norcocaine produced a decrease in blood pressure at lower doses, which reversed to a small increase at the higher dose. The higher dose of norcocaine clearly decreased heart rate and increased QRS duration. The cocaine metabolites benzoylecgonine and ecgonine.methyl ester increased blood pressure at the higher dose without affecting either heart rate or QRS duration. These results suggest that the accumulation of the persistent, active metabolites benzoylecgonine and ecgonine methyl ester may contribute to delayed-onset, cocaine-related toxicity.

Izzouki HK, Baum I, Goldberg SR, Schindler CW. Comparison of the effects of cocaine and its metabolites on cardiovascular function in anesthetized rats. J Cardiovas Pharmacol, in press.

Schindler CW, Wilkerson RD, Gillis RA, Foltin RW, Fischman MW, Newlin D, Levin, HR, Goldberg SR. Cardiovascular effects of cocaine: Underlying mechanisms. In: Harris L ed., Problems of Drug Dependence 1993, NIDA Research Monograph; in press.

Della S.R, Korupolu GR, Schindler CW, Goldberg S.R. Pathophysiological and pharmacological mechanisms of acute cocaine toxicity in conscious rats. J Pharmacol Exp Ther 1992; 262: 936-946.

Della SR, Goldberg SR. Monoamine uptake inhibitors alter pharmacokinetics of cocaine. Psychopharmacology, in press.

Della SR, Schindler CW, Goldberg SR. Chlorisondamine, a noncompetitive ganglionic blocker, antagonizes the cardiovascular effects of cocaine in conscious squirrel monkeys. Pharmacol Res 1993; 27: 233-239.

Della SR, Schindler CW, Goldberg, SR. Cocaine: Cardiovascular effects in relation to the inhibiton of peripheral neuronal monoamine uptake and the central stimulation of sympathoadrenal system. J Pharmacol Exp Ther, in press.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00012-05 BPGS

PERIOD COVERED

October 1 1992 to September 30 1993

TITLE OF PROJECT

Genetic Factors in Response to Acute and Chronic Drug Treatment

PRINCIPAL INVESTIGATOR

P.I.	RJ Marley	Senior Staff Fellow	Preclinical Pharmacology Laboratory
	SR Goldberg	Chief	Preclinical Pharmacology Laboratory
	LL Miner	Senior Staff Fellow	Preclinical Pharmacology Laboratory
	N Goodman	Research Pharmacologist	Preclinical Pharmacology Laboratory
	K Shimosato	Visiting Fellow	Preclinical Pharmacology Laboratory

COOPERATING UNITS

LAB/BRANCH

Preclinical Pharmacology Laboratory

SECTION

Behavioral Pharmacology

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER
1.6	1.1	0.5

CHECK APPROPRIATE BOXES

☐ (A) Human ☐ (b) Human Tissue ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

This project employed pharmacogenetic and neurochemical techniques to evaluate the contribution of genetic and environmental factors to individual differences in response to the chronic administration of drugs of abuse and to drugs proposed for the treatment of drug abuse. We are continuing to examine genetic differences in response to the convulsant and epileptogenic effects of cocaine. Having previously identified genetically distinct strains of mice that differ quantitatively and qualitatively in their response to chronic cocaine, as well as carbamazepine (CBZ), opiates and benzodiazepines, we are now using these models to study the mechanisms underlying the effects of the long-term administration of these drugs. To this end, we have examined neurochemical systems thought to be affected by these drugs. We have examined changes in GABAergic function following chronic treatment with benzodiazepine agonists and inverse agonists, naltrexone or cocaine and observed that there are genotypic differences in the homeostatic regulation of GABAergic function following chronic drug treatment. Characterization of receptor binding parameters for subtypes of opioid receptors in a number of inbred strains has revealed a strong genetic correlation between the number of mu and delta receptors in mouse brain. Studies of the effects of CBZ on cocaine seizures revealed that the efficacy of CBZ for inhibiting cocaine seizures increased with decreasing plasma and brain levels of CBZ suggesting that chronic carbamazepine induces the cytochrome P450-mediated metabolism of cocaine. We also conducted classical Mendelian cross analyses to examine genetic and environmental influences on morphine analgesia and found that genetic and environmental variables were acting to modulate genetic control of the analgesic response to morphine.

This project is scheduled to terminate at the end of FY93.

Marley RJ, Collins AC, Elmer GI, Sudakov SK, Belknap J, McClearn GE, Pickens RW, Goldberg SR. Genetic approaches to understanding the actions of drugs of abuse. In: Harris L ed. Problems of Drug Dependence 1992, NIDA Research Monograph, 132, 1993;47-51.

Marley RJ, Shimosato K, Elmer GI, Miner LL. Pharmacogenetic approaches to drug dependence. In: Wonnacott S, Lunt GG, Biochemistry of Drug Dependence. Portland Press, London, 1993; in press.

Marley RJ, Shimosato K, Frieman M, Goldberg SR. Time course for the development and persistence of the anticonvulsant effects of carbamazepine against cocaine seizures in three strains of mice. Brain Res 1993; 600:193-200.

Miner LL, Elmer GI, Pieper JO, Marley RJ. Aggression modulates genetic influences on morphine analgesia as assessed using a classical Mendelian cross analysis. Psychopharmacol 1993; 111:17-22.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00016-05 MPS

PERIOD COVERED

October 1 1992 to September 30 1993

TITLE OF PROJECT

Neurochemical Responses of Rats During Withdrawal of Cocaine or Saline

PRINCIPAL INVESTIGATOR

P.I.	N Pilotte	Staff Fellow	Neuroscience Branch
	MJ Kunar	Chief	Neuroscience Branch
	L Sharpe	Research Psychologist	Preclinical Pharmacology Laboratory
	E Cline	PRAT Fellow	Neuroscience Branch
	C Cerruti	Visiting Fellow	Neuroscience Branch

COOPERATING UNITS

Duke University

LAB/BRANCH

Neuroscience Branch

SECTION

Molecular Pharmacology

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER
3.5	3.5	0

CHECK APPROPRIATE BOXES

☐ (A) Human ☐ (b) Human Tissue ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

We continued our examination of the decrease in binding of the cocaine derivative [3H]WIN 35,428 to the dopamine (DA) transporter in homogenized striatum and nucleus accumbens at several times after a series of IV infusions of cocaine. The binding of [3H]WIN 35,428 was reduced by 30% in the nucleus accumbens 10, 30, and 60 days after of cocaine, but not 1, 3 or 6 days later or after saline. No change occurred in the striatum at any time. These data suggest that the DA transporters in the two regions may be regulated differently. We completed two related studies. The first is an autoradiographic study of [3H]WIN 35,428 binding in brains of rats injected IV with the isotope 1 or 10 days after the last IV infusion of cocaine. There was a significant 25% reduction in the in vivo [3H]WIN 35,428 binding in the nucleus accumbens of rats withdrawn from cocaine for 10 days. Secondly, we determined the distribution of the mRNA for the DA transporter using in situ hybridization in the brains of rats withdrawn from cocaine for 10 days. DA transporter mRNA was reduced in two nuclei of the ventral tegmental area that project to nucleus accumbens. The magnitude of the decrease in mRNA was similar to that of the decrease in transporter binding. The peptide neurotensin (NT) resides in part in the mesocorticolimbic DA neurons. Multiple IV infusions of cocaine decreased NT binding at their cell bodies but increased it markedly at their terminal fields. Ten days after withdrawal of cocaine, NT binding had recovered at the cell bodies, but binding at the terminal fields was enhanced further, suggesting that withdrawal from cocaine might decrease the synthesis and/or release of NT. Our preliminary findings show that NT accumulates in the prefrontal cortex and in the substantia nigra, the terminal fields of these neurons, 10 days after cocaine is withdrawn. It seems that these neurons synthesize NT after withdrawal of cocaine, but may not be able to release it. We are continuing to analyze the persistence of these changes. Taken together, these data show that long-lasting changes occur in dopaminergic neurons in reward-relevant areas in rat brain and may underlie other drug-related phenomena.

Cerruti C, Pilotte NS, Uhl G and Kuhar MJ. (1993) Reduction in Dopamine Transporter mRNA After Cessation of Chronic Cocaine Administration. Molecular Brain Research, in press.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00023-08 CDM

PERIOD COVERED

October 1 1992 to September 30 1993

TITLE OF PROJECT

Detection of Drugs of Abuse in Human Saliva

PRINCIPAL INVESTIGATOR

P.I.	EJ Cone	Chief	Clinical Pharmacology Branch
	WD Darwin	Chemist	Clinical Pharmacology Branch
	K Kato	Visiting Fellow	Clinical Pharmacology Branch
	D Yousefnejad	Chemist	Clinical Pharmacology Branch

COOPERATING UNITS

LAB/BRANCH

Clinical Pharmacology Branch

SECTION

Chemistry

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
0.9	0.7	0.2

CHECK APPROPRIATE BOXES

☒ (A) Human ☐ (b) Human Tissue ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

The presence of drugs of abuse in saliva of human subjects after drug administration was studied to determine the feasibility of drug testing with saliva as the biological specimen. Healthy subjects with a history of chemical substance abuse volunteered for these studies. Informed consent was obtained and all procedures were approved by the hospital Institutional Review Board. Following the administration of cocaine, marijuana or opiates, saliva and blood samples were collected periodically. Behavioral and physiological measures were made concurrently with collection of biological fluids. Samples were analyzed by radioimmunoassay and gas chromatography/mass spectrometry. Significant correlation's of blood levels with saliva levels were found for cocaine and opiates.

These studies provide the scientific basis for development of new non-invasive saliva tests for drugs of abuse.

Kato, K., Hillsgrove, M.J., Weinhold, L., Gorelick, D. A., Darwin, W.D. and Cone, E.J., Cocaine and Metabolite Excretion in Saliva Under Stimulated and Non-Stimulated Conditions. J. Anal. Toxicol., In Press, 1993.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00050-01 CNG

PERIOD COVERED

October 1 1992 to September 30 1993

TITLE OF PROJECT

Assessment of the Causes and Consequences of Drug Dependence

PRINCIPAL INVESTIGATOR

P.I.	R Pickens	Scientific Director	Office of the Director
	M LaBuda	Senior Staff Fellow	Office of the Director

COOPERATING UNITS

LAB/BRANCH

Office of the Director

SECTION

Clinical Neurogenetics

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
0.4	0.2	0.2

CHECK APPROPRIATE BOXES

☒ (A) Human ☐ (b) Human Tissue ☐ (c) Neither

☐ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK

The primary purpose of this research is to assess the consequences of drug dependence. Drug dependence is thought to have deleterious effects on the individual, producing severe social, behavioral, and medical consequences; however, efforts to quantify these effects have been hampered by a lack of information about the individual prior to drug use. As a result, it is often impossible to determine if an observed clinical condition is the result of drug dependence or is reflective of a preexisting condition. Discordant identical, or monozygotic, twins offer a unique means for assessing the adverse consequences of drug dependence. Because members of monozygotic twins are genetically identical, the study of twin pairs in which only one twin is drug dependent provides a powerful assessment of the effects of drug abuse while controlling for genetic variability. A secondary purpose of the study is the assessment of early experiential differences (both drug-related and non-drug related) to aid in the identification of non-shared environmental factors important in the development of drug dependence.

Through a larger twin study of the genetic influences on drug dependence conducted collaboratively by ARC investigators and Johns Hopkins University, are identifying twin pairs discordant for drug dependence willing to participate in the ARC Discordant Twin Study. The drug-abusing member of each twin pair is housed at the ARC residential unit for a 3-week drug-free period prior to study in order to distinguish between acute effects and long-term consequences of drug use. After this period, a variety of factors associated with drug dependence are assessed including: medical disorders and various metabolic and cardiovascular effects, personality and psychiatric status, neuropsychological performance, and early environmental experiences. Within-pair comparisons in each of these domains will significantly increase our knowledge concerning etiological factors important in drug dependence as well as the effects of long-term drug abuse.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00051-01 CNG

PERIOD COVERED

October 1 1992 to September 30 1993

TITLE OF PROJECT

Comorbidity between Alcohol, Drug, and Mental Disorders

PRINCIPAL INVESTIGATOR

P.I.	R Pickens	Scientific Director	Office of the Director
	M LaBuda	Senior Staff Fellow	Office of the Director

COOPERATING UNITS

LAB/BRANCH

Office of the Director

SECTION

Clinical Neurogenetics

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
0.4	0.2	0.2

CHECK APPROPRIATE BOXES

☒ (A) Human ☐ (b) Human Tissue ☐ (c) Neither

☐ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK

There is significant comorbidity between alcohol, drug and mental disorders in treatment samples and the general population. The basis of this phenomenon is not clear. The co-occurence of these disorders could be due to a common underlying genetic vulnerability or it could be the result of one disorder serving as an environmental influence that predisposes an individual to the other disorders. The elucidation of the etiology of the comorbidity would be important for prevention.

Twin cross-concordant data provide a method for assessing the cause of observed comorbidity. Twins are cross-concordant if one twin is affected with one disorder and the other twin is affected with a second disorder. If there are genetic factors common to both disorders, identical twins would be cross-concordant more often than would fraternal twins. If a significant difference is not found between identical and fraternal twins, the observed relationship between disorders is likely due to environmental factors.

Interpreting cross-concordance data is made difficult by two factors. First, cross-concordance may reflect the independent concordance for the second disorder that may exist within the twin pair. Secondly, cross-concordance may be the result of an environmental association between the two disorders in the cotwin.

Data on comorbid drug and mental disorders in twins with alcoholism will be combined with appropriate control data in order to explore methods of analyzing the etiology of the association between these disorders. Data are available on 169 same-sex twin pairs and analyses will range from simple cross-concordance comparisons to full bivariate cross-twin, cross-trait analysis.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00052-01 VUL

PERIOD COVERED

October 1 1992 to September 30 1993

TITLE OF PROJECT

The Discriminative Stimulus Effects of Drugs In Humans

PRINCIPAL INVESTIGATOR

P.I.	CE Johanson	Branch Chief	Etiology Branch
	K Preston	Section Chief	Treatment Branch
	JE Henningfield	Branch Chief	Clinical Pharmacology Branch
	R Lange	Clinical Director	Medical Affairs

COOPERATING UNITS

Clinical Trials Section
Clinical Pharmacology Branch

LAB/BRANCH

Etiology Branch

SECTION

Vulnerability

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER
0.8	0.2	0.6

CHECK APPROPRIATE BOXES

☒ (A) Human ☐ (b) Human Tissue ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

This project is designed to assess individual differences in reactions to drugs as measured by their discriminative stimulus effects. In addition, the differential modulation of these effects by environmental variables will be assessed. This series of studies is designed to understand individual differences in vulnerability as determined by differential reactions to drug effects and differential effects of modulating conditions.

The first study was designed to establish the drug discrimination methodology and explore the discriminative stimulus effects of an antihistamine. Twenty normal volunteers were trained to discriminate 75 mg tripelennamine from placebo. There were 33 experimental sessions. At the beginning of each session, subjects filled out mood questionnaires, performed performance tasks, their behavior was rated by observers, and they ingested a capsule. The assessment was repeated at regular intervals. Thirteen of the subjects learned the discrimination and nine of these were tested with additional drugs. Drugs that were identified as tripelennamine by over 75% of the subjects included diazepam and diphenhydramine and there was some evidence of dose related effects. Tripelennamine produced time related increases in diastolic blood pressure and heart rate as well as increases on subjective effects scales indicating sedative like effects. Similar effects were seen with the drugs that substituted although diazepam had different physiological effects. Amphetamine was tested as a negative control but over half of the subjects discriminated both doses as tripelennamine. Its physiological effects were similar to tripelennamine but its subjective effects were placebo like. These results indicate that tripelennamine has subtle or ambiguous discriminative stimulus effects, making it an ideal compound to use in further studies designed to look at vulnerability and modulatory environmental conditions.

In two ongoing studies, the same experimental design is being used to assess the influence of instructional control or context. The instructions or context (performance tasks) are designed to bias subjects towards experiencing sedative like effects in one situation or stimulant like effects in another.

Evans, S., Henningfield, J, and Johanson, C.E. Discriminative stimulus effects of tripelennamine in humans. In, Problems of Drug Dependence 1993, Harris, L.S. (ed), National Institute on Drug Abuse Monograph Series, in press.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00054-03 VUL

PERIOD COVERED

October 1 1992 to September 30 1993

TITLE OF PROJECT

Infants Exposed to Cocaine in Utero

PRINCIPAL INVESTIGATOR

P.I.	CE Johanson	Branch Chief	Etiology Branch
	PW Suess	IRTA	Etiology Branch
	R Herning	Research Psychologist	Medical Affairs

COOPERATING UNITS

J Dipierto, Maternal and Child Health, JHU

LAB/BRANCH

Etiology Branch

SECTION

Vulnerability

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
0.7	0.2	0.5

CHECK APPROPRIATE BOXES

☒ (A) Human ☐ (b) Human Tissue ☐ (c) Neither

☒ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK

Fetal cocaine exposure has been reported to have effects on newborn neurobehavior, sleep and state regulation, and EEG patterns. Early mother-infant interactions have also been shown to be disrupted among drug exposed dyads. Central nervous system development continues postnatally in humans and can be influenced by environmental factors such as maternal interactions. Maternal interactions facilitate the development of self regulation during the newborn period. The purpose of this study is to investigate central nervous system development in infants exposed to cocaine in utero and the contribution of variation in maternal interactions to this development. Both cardiac and electroencephalographic indices of CNS development are being assessed at conceptual ages of 40, 48, and 56 weeks. Mother-infant interactions are being observed at 48 and 56 weeks.

Mothers and their infants are recruited from area full-term newborn nurseries based on toxicology and self reports of cocaine use during pregnancy. Newborns are tested for cardiac reactivity to an auditory stimulus while still in the nursery. Infant cardiac and sleep EEG are then assessed at the ARC at the specified follow-up ages. Mother-infant interactions are videotaped during a face-to-face play interaction and during a feeding. Additional assessments of infant reactivity and temperament as well as maternal psychopathology are collected by maternal questionnaire.

Comparisons of cardiac vagal tone and heart rate, spectral components and patterns of sleep EEG and sleep state distribution, between cocaine exposed and unexposed, full-term, SES matched infants will be conducted. These analyses will detect differences in CNS development during these infants' first 4 months and establish the contributions of both in utero cocaine exposure and maternal interactions.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00060-01 VUL

PERIOD COVERED

October 1 1992 to September 30 1993

TITLE OF PROJECT

Vulnerability to Substance Abuse Challenge

PRINCIPAL INVESTIGATOR

P.I.	DB Newlin	Research Psychologist	Etiology Branch
	CE Johnason	Branch Chief	Etiology Branch

COOPERATING UNITS

Molecular Neurobiology Branch
Neuroscience Branch

LAB/BRANCH

Etiology Branch

SECTION

Vulnerability

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
0.3	0.1	0.2

CHECK APPROPRIATE BOXES

☒ (A) Human ☐ (b) Human Tissue ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

This project concerns the subjective and physiological responses to drug challenges among individuals at different levels of risk for substance abuse. The high risk participants have either a documented first degree family history of alcoholism, or possess dopamine D2 receptor gene polymorphisms that may confer genetic risk for substance abuse. The low risk participants are sampled from similar populations, but do not possess these characteristics. These high risk individuals are old enough (21 to 25 years) to have had some alcohol experience, but are screened to rule out current or past alcohol abuse or dependence.

Participants are exposed to drug challenges that include oral alcohol in a moderate dose, and on separate occasion, a low dose of oral methylphenidate. The alcohol challenges are presented at the same dose on different days in order to assess the development of chronic tolerance and/or sensitization, and to determine the reliability and stability of the subjective and cardiovascular responses to alcohol. The methylphenidate challenges are presented to some participants at several different dosages (including placebo) on different days in order to assess the dose dependency of these pharmacological effects.

Results indicate that participants with family histories of alcoholism demonstrate greater "reward" from alcohol, reflected in larger subjective responses to alcohol in positive mood, more general motor activation, and greater stress response dampening in hormonal responses to the drug. Preliminary results with methylphenidate indicate measurable responses to the drug, but a slightly higher dose has been added to the protocol to achieve more robust subjective and cardiovascular effects so that differences as a function of risk for substance abuse may be detected more effectively.

This project is scheduled to terminate at the end of FY94.

Smith, S.S., Newman, J.P., Evans, A., Pickens, R., Wydeven, J., Uhl, G.R., & Newlin, D.B. (1993). Comorbid psychopathy is not associated with increased D2 dopamine receptor Taq I A or B gene markers in incarcerated substance abusers. Biological Psychiatry, 33, 845 848.

Newlin, D.B. (1993). In the belly of the beast: Toward a motivation view of addiction. Contemporary Psychology, in press.

Newlin, D.B. (1993). Alcohol challenge with high risk individuals. In Zucker, Howard, & Boyd (Eds.), Development of alcohol problems: Exploring the biopsychosocial matrix of risk. NIAAA Monograph, in press.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00061-01 VUL

PERIOD COVERED

October 1 1992 to September 30 1993

TITLE OF PROJECT

Etiologic Factors in the Initiation of Drug Use

PRINCIPAL INVESTIGATOR

P.I.	H Chilcoat	Staff Fellow	Etiology Branch
	C Schutz	Visiting Fellow	Etiology Branch
	CE Johanson	Branch Chief	Etiology Branch
	J Anthony	Senior Staff Fellow	Etiology Branch

COOPERATING UNITS

LAB/BRANCH

Etiology Branch

SECTION

Vulnerability

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
2.8	10	1.8

CHECK APPROPRIATE BOXES

☒ (A) Human ☐ (b) Human Tissue ☐ (c) Neither

☒ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK

In order to develop effective strategies for preventing drug use and related problems, it is critical that factors playing a causal role in drug use be identified. Of particular interest are causal factors that are malleable and potential targets of intervention. Etiologic risk factors can be most effectively identified using longitudinal studies of children, who are passing through the period of high risk for initiation of drug use.

In this longitudinal research, it is necessary to consider drug use outcomes as they occur through different developmental stages. For example, drinking a beer is more normative for a high school senior than it is for a 10 year old child. In addition, factors that are protective in childhood might not be protective later in adolescence. For this reason, the Etiology Branch is involved in a longitudinal study of an epidemiologically defined sample of urban children. Data from this study will enable the identification of factors that play a causal role in the onset of early drug use and subsequent problems related to use of psychoactive substances as they develop through childhood and adolescence.

Current research is addressing the role of parenting behavior, in particular parent monitoring and supervision of a child's activities, in relation to early drug sampling and later more problematic drug use. Future research will investigate the role of neighborhood factors in the development of drug use and will examine the potential causal and mediating effects of peer drug use and level of antisocial behavior in relation to other risk factors at different stages of drug use and different points in the life span. In addition, another project is currently underway that employs a multistage sampling design to assess the comorbidity between drug use and depression. The combination of longitudinal follow-up of this epidemiologic sample with more intensive measures administered on a screened subset of this sample will enable a more thorough understanding of drug use and both its causes and consequences.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00062-01 VUL

PERIOD COVERED

October 1 1992 to September 30 1993

TITLE OF PROJECT

Epidemiologic Research Methods

PRINCIPAL INVESTIGATOR

P.I.	H Chilcoat	Staff Fellow	Etiology Branch
	C Schutz	Visiting Fellow	Etiology Branch
	CE Johanson	Branch Chief	Etiology Branch

COOPERATING UNITS

LAB/BRANCH

Etiology Branch

SECTION

Vulnerability

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
1.1	0.6	0.5

CHECK APPROPRIATE BOXES

☒ (A) Human ☐ (b) Human Tissue ☐ (c) Neither

☐ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK

A primary concern in epidemiologic studies of drug abuse is the development of measurement strategies that are reliable and valid. Not only is it important to develop effective measures of drug abuse outcomes, but it is also necessary to obtain reliable, unbiased measures of related risk factors. Methodologic studies designed to address these concerns will increase confidence in estimates of prevalence and incidence of drug abuse as well as producing indicators of association that are unlikely to be biased. Little is currently known about the reliability of instruments that measure problems related to the use of illicit drugs. In particular, there is a relative dearth of information pertaining to test-retest reliability, although there are a number of studies that have examined inter-rater reliability. However, test-retest reliability is a prerequisite to inter-rater reliability. For this reason, the Etiology Branch is undertaking a test-retest study that is designed to assess the reliability of the substance abuse supplement to the 1991 National Health Interview Survey. This questionnaire consists of 122 items that assess the use of various drugs in the lifetime and last year, then specifically addresses problems related to the use of marijuana and cocaine. Two hundred individuals who enter the recruitment process at the ARC will complete the questionnaire at baseline and three weeks later. A random sample of one-half of these participants will be asked to complete an additional questionnaire two hours after responding to the first questionnaire. The test-retest reliability of individual items will be analysed. as well as the reliability of counts of symptoms or diagnostic categories based on combinations of symptoms. Another important concern in the conduct of field studies of drug abuse is the impact of the interview environment on self-reports of drug use. A study that was recently completed in the Branch using data from the 1990 National Household Survey on Drug Abuse (NHSDA) found that adolescents (12-17 years old) were less likely to report use of licit and illicit drugs if a parent was present during the interview but no difference if another person was present. This finding has implications for the conduct of future household surveys. Other methodologic issues addressed in this project include development and application of statistical methods relevant to drug abuse research. One recently completed project developed a statistical procedure for producing multi-dimensional confidence regions for depicting uncertainty around parameter estimates in conditional logistic regression.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00065-03 BDS

PERIOD COVERED

October 1 1992 to September 30 1993

TITLE OF PROJECT

Development of a New Psychometric Instrument for Assessing Drug Cravings

PRINCIPAL INVESTIGATOR

P.I.	EJ Singleton	Senior Staff Fellow	Clinical Pharmacology Branch
	JE Henningfield	Chief	Clinical Pharmacology Branch

COOPERATING UNITS

LAB/BRANCH

Clinical Pharmacology Branch

SECTION

Biology of Dependence

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
2	1	1

CHECK APPROPRIATE BOXES

☒ (A) Human ☐ (b) Human Tissue ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

Among the most ubiquitous effects of addictive drugs, but least well studied, is drug craving. There has not even existed a validated psychometric instrument for the evaluation of craving that would lend itself to the systematic development of medications for treating drug craving. The Addiction Research Center is presently developing such instrumentation for cocaine, heroin, and alcohol and other drugs of abuse. This research should help us to identify mechanisms of addictive action which are common across drug classes and therefore lead to a better understanding of the mechanisms which underlie the drug cravings. Our initial findings indicated that cocaine craving is a multidimensional construct, involving an admixture of urges and desire, intent to use, loss of control over use, and anticipation of positive outcome. A similar multidimensional structure was found among responses from subjects evaluated using the heroin instrument. One hundred and-sixty subjects have completed the new Alcohol Craving Questionnaire. The project was modified in June 1993 to include measurement of craving and psychomotor/cognitive testing for outpatient research volunteers and those on the residential unit as a secondary study to examine the relationship between drug cravings and human performance. The Marijuana Craving Questionnaire is under development for administration in FY 1994. The utility of computer administration of the series will be assessed to improve the
efficiency of the testing. Finally, to extend the generality of the research and investigate ethnic and cultural factors, a Standard Spanish version of the Cocaine Craving Questionnaires and Manual has also been developed.

These advances in instrument development and the enhanced understanding of craving should enable more rapid progress in the ability to produce more selective and efficacious medications and other interventions to meet the needs of a those addicted to drugs. With these instruments we should be able to predict which craving dimensions may be relieved by medications and which will require other intervention to enable the person to achieve and sustain drug abstinence.

iffany ST, Singleton EG, Henningfield JE, Haertzen CA. The development of a cocaine craving uestionnaire. Journal of Alcohol and Drug Dependence, in press.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00066-05 CDM

PERIOD COVERED

October 1 1992 to September 30 1993

TITLE OF PROJECT

Fast Action Dynamics of Marijuana

PRINCIPAL INVESTIGATOR

P.I.	EJ Cone	Chief	Clinical Pharmacology Branch
	WD Darwin	Chemist	Clinical Pharmacology Branch

COOPERATING UNITS

LAB/BRANCH

Clinical Pharmacology Branch

SECTION

Chemistry

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
0.2	0.1	0.1

CHECK APPROPRIATE BOXES

☒ (A) Human ☐ (b) Human Tissue ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

Although early changes which occur during the smoking of marijuana are more likely to be indicative of its mode of action, the smoking phase of marijuana use has largely been ignored and very little is known regarding what happens to a human subject during this process.

This study detailed the effects of smoking marijuana cigarettes on a variety of systems including psysiologic effects, behavior and hormonal systems. In addition, blood and saliva levels were determined during and after smoking. Blood and saliva levels were compared to drug-induced effects and hormonal changes.

The results from this study provide a comprehensive assessment of marijuana s effects that occur both during and after smoking and offer important insight to the mode of action of this widely abused drug.

Cone, E. J., and Huestis, M. A. Do Consecutive Urine Catches Differ in Marijuana Metabolite Concentration? J. Anal. Toxicol., 17: 186-187, 1992.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00073-02 MPS

PERIOD COVERED

October 1 1992 to September 30 1993

TITLE OF PROJECT

Anorectic Effects of Metabolites of MDA and MDMA

PRINCIPAL INVESTIGATOR

P.I. SY Yeh Pharmacologist Neuroscience Branch

COOPERATING UNITS

LAB/BRANCH

Neuroscience Branch

SECTION

Molecular Pharmacology

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
1.2	1	0.2

CHECK APPROPRIATE BOXES

☐ (A) Human ☐ (b) Human Tissue ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

We have observed that body weight of rats was decreased after administration of the metabolites of 3,4-methyledioxyamphetamine (MDA) and N-methyl-3,4-methylenedixoyamphetamine (MDMA) during a study of the neurochemical effects of MDA and MDMA, analogues of amphetamine and methylamphetamine, respectively. Preliminary results of the anorexia of MDMA, N-ethyl-3,4-methylenedioxyamphetamine (MDEA), amphetamine, 4-hydroxyamphetamine, phenylpropanolamine, phenylephrine, sigma-methyldopamine, sigma-methylepinephrine, sigma-methylnorepinephrine have been obtained in 1992. Additional experimental data on anorectic effect of these compounds in rats have been collected. Furthermore, the anorectic and stimulatory effects of metaraminol has been studied. From the results of these studies the following conclusions may be drawn: 1) Anorectic potency of MDMA and MDEA are comparable to that of amphetamine. 2) Anorectic potency of monohydroxy derivatives of amphetamine, such as 4-hydroxyamphetamine and phenylpropanolamine, decreased as compared to that of amphetamine. 3) The anorectic potency of dihydroxy derivatives of amphetamine, such as phenylephrine, is higher than that of monohydroxy derivative of amphetamine and comparable to that of amphetamine. 4) The anorectic potency of three hydroxy derivatives of amphetamine and methamphetamine, such as sigma-methylepinephrine and sigma-methylnorepinephrine, respectively, are potent and long last than that of amphetamine. Stimulatory activity of hydroxylated derivatives of amphetamine is less than that of amphetamine. Application for patent for sigma-methylepinephrine, sigma-methylnorepinephrine and metaraminol for use as anorectic agents and treatment of obesity has been filed.

UBLICATIONS

eh, S.Y. Use of sigma-methylepinephrine and sigma-methylnorepinephrine as anorectic agents and treatment f obesity. Filed in the U.S. Patent and trademark Office, June 30, 1992.

eh, S.Y. Composition and Method for Weight Reduction in Mammals. Filed in the U.S. Patent and Trademark)ffice, March 25, 1993 and in PCT international Patent and Trademark Office, June 30, 1993.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00076-02 MNS

PERIOD COVERED

October 1 1992 to September 30 1993

TITLE OF PROJECT

Dopamine Transporter I: Structure/Function Releationships and Molecular Modeling

PRINCIPAL INVESTIGATOR

P.I.	JB Wang	Guest Worker	Molecular Neurobiology Branch
	GR Uhl	Branch Chief	Molecular Neurobiology Branch
	S Davis	IRTA	Molecular Neurobiology Branch
	C Surratt	Senior Staff Fellow	Molecular Neurobiology Branch

COOPERATING UNITS

S Yuhaz, M Amsel, Johns Hopkins Univ.

LAB/BRANCH

Molecular Neurobiology Branch

SECTION

Molecular Neurobiology

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
1.5	1.5	0

CHECK APPROPRIATE BOXES

☐ (A) Human ☐ (b) Human Tissue ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

The dopamine transporter (DAT) has been identified as the cocaine receptor most linked with psychostimulant reward and reinforcement in the brain. Cloning DAT cDNAs from rat and man by Addiction Research Center molecular neurobiologists in previous FYs has allowed testing of the roles of discrete residues in the recognition of dopamine, cocaine and their analogs using site-directed mutagenesis. These approaches were especially explored in order to seek transporter regions selectively involved in cocaine binding and not in dopamine transport, a potential aid in development of anti-cocaine therapeutics. Elucidation of regions selectively involved in neurotoxin uptake but less implicated in dopamine uptake could yield sites for potential selective neurotoxin blockers.

Analyses of over 30 dopamine transporter mutants, most prepared and analyzed over the last FY, has continued to yield interesting results. Replacement of a tyrosine located in transmembrane domain 4 yielded enhanced Km for dopamine uptake and substantially reduced affinity for cocaine analog, for example. Molecular modeling of the transporter has facilitated identification of targets for mutagenesis, and has provided useful scenarios for cocaine-transporter interactions. Analyses of mutants in several transmembrane regions and in extracellular domains documents several molecular regions at which cocaine and dopamine recognition sites can be separated.

Uhl GR, Hartig PR. Transporter explosion: update on uptake, TIPS 1992;13(12):421-5.

Kitayama S, Wang J-B, Uhl GR. Dopamine transporter mutants selectively enhancing MPP+ transport, Synapse 1993;in press.

Surratt CK, Wang J-B, Yuhasz S, Amzel M, Kwon HM, Handler JS, Uhl GR. Sodium- and chloride-dependent transporters in brain, kidney, and gut: lessons from cDNA cloning and structure-function studies, Curr Opin Nephrol Hyper 1993;in press.

Uhl GR, Kitayama S, Gregor P, Nanthakumar E, Persico A, Shimada S. Neurotransmitter transporter family cDNAs in a rat midbrain library: 'orphan transporters' suggest sizable structural variations, Mol Brain Res 1992;16:353-9.

Gregor P, Patel A, Shimada S, Lin C-L, Rochelle JM, Kitayama S, Seldin MF, Uhl GR. Murine serotonin transporter: sequence and localization to chromosome 11, Mammalian Genome 1993;4:283-4.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00077-02 MNS

PERIOD COVERED

October 1 1992 to September 30 1993

TITLE OF PROJECT

Dopamine Transporter III: Expression, Cellular Distribution & Regulation

PRINCIPAL INVESTIGATOR

P.I.	C Surratt	Senior Staff Fellow	Molecular Neurobiology Branch
	GR Uhl	Branch Chief	Molecular Neurobiology Branch
	C Freed	Guest Worker	Molecular Neurobiology Branch
	F Kaddis	Guest Worker	Molecular Neurobiology Branch
	S Kitayama	Visiing Fellow	Molecular Neurobiology Branch

COOPERATING UNITS

R Vaughn, C Cerruti, M Kuhar, Neuroscience Branch
S Shimada, Osaka Univ School of Medicine
F Javoy-Agid, Hospital Salpietriere, Paris

LAB/BRANCH

Molecular Neurobiology Branch

SECTION

Molecular Neurobiology

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
0.85	0.85	0

CHECK APPROPRIATE BOXES

☐ (A) Human ☐ (b) Human Tissue ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

The dopamine transporter/cocaine receptor (DAT) is the site at which cocaine exerts rewarding/reintorcing effects. Cloning of rat and human transporter cDNAs provided primary sequence information and cDNA clones that facilitated production of antibodies that allow detection of the transporter protein immunoreactivity and mRNA expression in tissue extracts and in tissue sections, retining our information about the cellular distribution of transporter expression.

Conjugated peptide preparations and biosynthesized fusion protein fragments elicited antibody responses in immunized rabbits; one of these sera recognized the transporter in immunohistochemical analyses. In situ hybridization studies continued to suggest high levels of transporter mRNA expression in neurons of the substantia nigra pars compacta and somewhat lower levels of expression in neurons of the ventral tegmental area in both rat and human. Retinal and arcuate nucleus neurons expressed even lower levels of mRNA in rats. Immunohistochemical studies revealed dense transporter immunoreactivity in fine, beaded neural processes found densely in the striatum and nucleus accumbens, but significantly less cell body staining than that found in adjacent control sections stained for tyrosine hydroxylase. Study of both coexpressed mRNAs revealed less tyrosine hydroxylase mRNA expression that transporter mRNA expression, despite good coregistration of expression. Studies of development revealed initial mRNA expression in ventral midbrain as early as embryonic day 14, with steadily increasing expression until adult levels were reached after birth. This work confirms the exquisitely cell-specific expression of this gene in zones that include the mesolimbic/mesocortical neurons important for reward and reinforcement, suggests a prominent and rapid distribution of transporter protein away from the perikaryon soon after synthesis, and indicates the possibility of significant developmental effect of cocaine on transporter expressed in utero.

Transporter mRNA in cocaine-treated and withdrawn animals displayed moderate downregulation in cells of the midline ventral tegmental area. This observation correlates with data on reduced nucleus accumbens transporter binding densities, and suggests a specific mechanism that could contribute to cocaine "craving" and other clinical withdrawal phenomena.

rruti C, Walther DM, Kuhar MJ, Uhl GR. Dopamine transporter mRNA expression is intense in rat midbrain
trons and modest outside midbrain, Mol Brain Res 1993;18:181-6.

rsico AM, Schindler CW, Brannock MT, Gonzalez AM, Surratt CK, Uhl GR. Dopaminergic gene expression
ing amphetamine withdrawal, NeuroReport 1993;4(1):41-4.

ita M, Shimada S, Nishimura T, Uhl G, Tohyama M. Ontogeny of dopamine transporter mRNA expression in
rat brain, Mol Brain Res 1993;in press.

rruti C, Pilotte NS, Uhl G, Kuhar MJ. Reduction in dopamine transporter mRNA after cessation of repeated
caine administration, Mol Brain Res 1993;in press.

GR. Elucidating neurotensin receptor cDNAs and their distribution. In: Kitabgi P, Nemeroff C, eds. The
urobiology of neurotensin. New York: Annals of The New York Academy of Sciences, 1992;101-8.

GR. Neurotransmitter and drug receptor genes. In: Molecular approaches to drug abuse research:
ckville, MD: Dept. of Health and Human Services, National Institute on Drug Abuse Research Monograph,
. 2, 126, 14-22, 1992.

ughan RA, Uhl G, Kuhar MJ. Recognition of dopamine transporter by antipeptide antibodies, Mol Cell
urosci 1993;4:209-15

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00079-02 MNS

PERIOD COVERED

October 1 1992 to September 30 1993

TITLE OF PROJECT

Dopamine Transporter II: Structure/Function Relationships & Posttranslational Mod

PRINCIPAL INVESTIGATOR

P.I.	JB Wang	Guest Worker	Molecular Neurobiology Branch
	GR Uhl	Branch Chief	Molecular Neurobiology Branch
	S Davis	IRTA	Molecular Neurobiology Branch
	C Surratt	Senior Staff Fellow	Molecular Neurobiology Branch

COOPERATING UNITS

S Kitayama, T Dohi, Hiroshima Univ School of Med

LAB/BRANCH

Molecular Neurobiology Branch

SECTION

Molecular Neurobiology

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
0.66	0.66	0

CHECK APPROPRIATE BOXES

☐ (A) Human ☐ (b) Human Tissue ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

The dopamine transporter (DAT) has been identified as the cocaine receptor most linked with psychostimulant reward and reinforcement in the brain. Cloning DAT cDNAs from rat and man by Addiction Research Center molecular neurobiologists in previous FYs has allowed testing of the roles of discrete residues in the recognition of dopamine, cocaine and their analogs using site-directed mutagenesis. These approaches have allowed elucidation of residues likely to be involved in posttranslational modifications of the transporter, and in the functions mediated by posttranslational alterations. These approaches were especially explored in order to seek transporter regions and functions selectively involved in cocaine binding and not in dopamine transport, a potential aid in development of anti-cocaine therapeutics.

Cysteine and asparagine residues that may be required for posttranslational maturation of DAT structure and polar or highly conserved residues within transmembrane regions have been identified during this FY. Mutant analyses revealed that each of the four sites for N-linked glycosylation appears to be utilized, and that significant amounts of glycosylation are essential for full transporter function. Cysteine residues at positions 180 and 189 were each found to each be necessary for DAT function, indicating the possible presence of an intramolecular disulfide bond that could provide secondary and tertiary structural constraints to this portion of the transporter.

Studies with phorbol esters and forskolin indicated that phosphorylation by protein kinase C, but not protein kinase A, reduced transporter function in both cocaine analog recognition and dopamine uptake. Mechanisms were different, however: velocity of transport, and affinity of binding were altered.

Patel A, Uhl G, Kuhar MJ. Species differences in dopamine transporters: postmortem changes and glycosylation differences, J Neurochem 1993;61:496-500.

Kitayama S, Dohi T, and Uhl GR. Phorbol esters alter functions of the expressed dopamine transporter, Eur J Pharmacol 1993;in press.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00083-02 MNS

PERIOD COVERED

October 1 1992 to September 30 1993

TITLE OF PROJECT

NMDA Neurotoxicity: Mediation by NO and Other Mechanisms

PRINCIPAL INVESTIGATOR

P.I.	V Dawson	IRTA	Molecular Neurobiology Branch
	G Uhl	Branch Chief	Molecular Neurobiology Branch
	T Dawson	Instructore	Johns Hopkins University
	S Snyder	Director	Johns Hopkins School of Medicine

COOPERATING UNITS

Dept. of Neuroscience, Johns Hopkins

LAB/BRANCH

Molecular Neurobiology Branch

SECTION

Molecular Neurobiology

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
1.18	1.18	0

CHECK APPROPRIATE BOXES

☐ (A) Human ☐ (b) Human Tissue ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

Abused substances produce long-term brain changes including neurotoxicity, through mechanisms that are largely unknown. The candidate neuromodulator nitric oxide (NO) can mediate aspects of NMDA-induced neurotoxicity in vivo and in primary cultured neurons. In this FY, we have extended observations made during the previous fiscal year that show that in situations of excess glutamate stimulation, NO mediates cell death in culture and therefore may mediate the cellular destruction observed following stroke, brain injury, neurodegenerative diseases, and severe drug abuse.

Mature primary culture neurons were exposed to various drug solutions and the resultant cell death was assayed. NMDA neurotoxicity was found in rat primary cell cultures of cortex. Modulating the activity of the NO-synthetic enzyme nitric oxide synthetase (NOS) by inhibiting its cofactor calmodulin, by changing its phosphorylation state or by inhibiting the shuttling of electrons through its flavoproteins modulates NMDA neurotoxicity: as NOS activity is decreased so is neurotoxicity. The toxicity of the HIV-coat protein, gp120, can also be attenuated with inhibitors of NOS.

PUBLICATIONS

Dawson VL, Dawson TM, Bartley DA, Uhl GR, Snyder SH. Mechanisms of nitric oxide-mediated neurotoxicity in primary brain cultures, J Neurosci 1993;13:2651-61.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00084-02 GS

PERIOD COVERED

October 1 1992 to September 30 1993

TITLE OF PROJECT

Biochemical Consequences of Brain Region Specific Expression

PRINCIPAL INVESTIGATOR

P.I.	DM Donovan	Senior Staff Fellow	Molecular Neurobiology Branch
	GR Uhl	Branch Chief	Molecular Neurobiology Branch
	D Walther	Biologist	Molecular Neurobiology Branch
	M Perry	Biologist	Molecular Neurobiology Branch

COOPERATING UNITS

C Schindler, Preclinical Pharmacology Branch

LAB/BRANCH

Molecular Neurobiology Branch

SECTION

Genetics

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
1.26	0.76	0.56

CHECK APPROPRIATE BOXES

☐ (A) Human ☐ (b) Human Tissue ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

There are large individual differences among humans and animals in behavioral, physiological and toxicological responses to drugs of abuse. Many of these individual differences in behavioral responses to drugs display substantial genetic components. Transgenic animals provide means for approaching three interrelated goals: 1) Identification of gene elements that confer cell-type specific expression and may thus allow targeting of introduced genetic material to appropriate brain regions; 2) Elucidation of gene elements yielding transsynaptic gene regulation and thus allowing appropriate regulated expression of introduced genetic material; and 3) Ascertainment of biochemical and behavioral consequences of the introduction of or disruption of specific genes.

Dopaminergic systems' involvement in central mechanisms of reward and reinforcement, and involvement of pre- and post-synaptic opioid peptide systems in the effects of opiate drugs has led to focus on these systems during this FY. Elements in the dopamine transporter gene's 5' flanking region that might confer its exquisite dopamine cell-specific expression were sought by cloning more than 20 kb of this sequence, and examining expression in different cultured cells and in transgenic animals. Tyrosine hydroxylase promoter, which can provide catecholamine-specific gene expression, was used to drive expression of dopamine transporter, interesting transporter mutants, and mu opiate receptor cDNAs. Preliminary analyses appear to reveal brain expression of mRNA but less expression of protein, while initial behavioral studies indicate a variable influence of transporter overexpression on exploratory, habituation, and cocaine-responsive behaviors.

Uhl GR, Takemura M. Gene mechanisms in primary afferent proenkephalin regulation in nucleus caudalis. In: Inoki R, Shigenaga Y, Tohyama M, eds. Processing and inhibition of nociceptive information. The Netherlands: Elsevier Science Publishers B.V., 1992;103-8.

Uhl GR. A review of insitu hybridization techniques: relevance to combined immunocytochemical studies. In: Cuello AC, ed. Immunohistochemistry. England: John Wiley & Sons, 1993;Second Edition, Chapter 9, 281-300.

Marota JAJ, Crosby G, Uhl GR. Selective effects of pentobarbital and halothane on c-fos and jun-B gene expression in rat brain, Anesthesiology 1992;77:365-71.

Walther D, Takemura M, Uhl G. FOS family member changes in nucleus caudalis neurons after primary afferent stimulation: enhancement of fos B and c-fos, Mol Brain Res 1993;17:155-9.

Uhl GR. Identifying and localizing gene expression important for the actions of abused drugs. In: London L, ed. Imaging drug action in the brain. Boca Raton: CRC Press, 1993;14:379-404.

Crosby G, Marota JJA, Uhl GR. Preproenkephalin gene expression in rat spinal cord following subarachnoid analgesia with morphine or clonidine, Anesthesiology 1993; n press.

O'Hara BF, Donovan DM, Lindberg I, Brannock MT, Ricker DD, Moffatt CA, Klaunberg BA, Schindler C, Chang TSK, Nelson RJ, Uhl GR. Proenkephalin transgenic mice: analysis of testicular expression and function, Mol Cell Endocrinol 1993;submitted.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00086-02 MNS

PERIOD COVERED

October 1 1992 to September 30 1993

TITLE OF PROJECT

Psychostimulant Effects in Humans with Dopamine Lesions

PRINCIPAL INVESTIGATOR

P.I.	GR Uhl	Branch Chief	Molecular Neurobiology Branch
	A Persico	Visiting Fellow	Molecular Neurobiology Branch

COOPERATING UNITS

M Kuhar, Neuroscience Branch
J Henningfield, Clinical Pharmacology Branch

LAB/BRANCH

Molecular Neurobiology Branch

SECTION

Molecular Neurobiology

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER
0.11	0.11	0

CHECK APPROPRIATE BOXES

☒ (A) Human ☐ (b) Human Tissue ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

Lesions studies in experimental animals document important roles for mesolimbic/mesocortial dopamine neurons lying in the ventral tegmental area in the reinforcing and rewarding properties of psychostimulants, and perhaps of other drugs of abuse. To test whether this "dopamine hypothesis" of psychostimulant reward is valid in humans, we examined psychostimulant effects on subjective ratings of mood in normal individuals and those with the dopamine cell lesions of Parkinson's disease. Prior anatomic studies suggest that ca. 60% of VTA neurons may be depleted in these brains, although the damage to the substantia nigra dopamine systems is greater.

Subjective rating scales of mood, cardiovascular parameters, and locomotor functional ratings were performed after oral doses of placebo or methylphenidate using standard methods. Evidence for reduced responses in the Parkinson's disease subjects included significant reductions in methylphenidate-induced "good" feeling ratings on visual analog scales, and trends toward reductions in several associated measures in comparison to age- race- and sex-matched controls. These findings support dopaminergic theories of psychostimulant reward/reinforcement in humans.

Future work will attempt to detect whether other individuals with dopamine system damage due to other pathologies share blunted methylphenidate responsiveness. Individuals with different levels of damage as assessed by PET studies of dopamine transporter density, will also be evaluated.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00087-02 MNS

PERIOD COVERED

October 1 1992 to September 30 1993

TITLE OF PROJECT

Psychostimulant Effects of Gene Expression

PRINCIPAL INVESTIGATOR

P.I.	A Persico	Visiting Fellow	Molecular Neurobiology Branch
	L Miner	Senior Staff Fellow	Molecular Neurobiology Branch
	D Vandenbergh	Senior Staff Fellow	Molecular Neurobiology Branch
	RJ Marley	Senior Staff Fellow	Molecular Neurobiology Branch

COOPERATING UNITS

A Gonzales, Dept of Neuroscience, JHU
C Schindler, Preclinical Pharmacology Branch
R Zaczek, Dupont-Merch Pharmaceuticals

LAB/BRANCH

Molecular Neurobiology Branch

SECTION

Molecular Neurobiology

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
1.16	1.16	0

CHECK APPROPRIATE BOXES

☐ (A) Human ☐ (b) Human Tissue ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

Tolerance, sensitization, withdrawal and craving can be viewed as events acquiring storage of information in the central nervous system. Long-term storage of information is increasingly tied to alterations in gene expression which can be modulated by alterations in the expression or activities of transcription factors. The expression of transcription factors and transcription factor gene targets can change following acute and chronic psychostimulant treatments. These studies have now been extended: 1) Studies identifying brain-region-specific patterns of psychostimulant-induced change in transcription factor mRNAs in single rodent strains were correlated with behavioral and neurotransmitter turnover measures. 2) Since pharmacogenetic techniques have proven valuable in examining mechanisms underlying various drug responses, the effects of psychostimulant treatments on the expression of several transcription factor genes in inbred strains of mice known to differ in their initial sensitivity to cocaine were examined. 3) Modulation of genes of dopaminergic neurotransmission was examined in several psychostimulant paradigms. 4) Since many of the genes whose modulation might be important for drug responses may be currently unknown, Differential Display Polymerase Chain Reaction (DDPCR) has been employed to identify genes whose expression is changed during psychostimulant treatment and withdrawal.

Evidence for tolerance, sensitization, withdrawal and cross-tolerance with injection stress was recorded at the level of transcription factor gene expression. These temporal patterns closely resembled changes in striatal dopamine turnover, while decreases in novelty-responses stereotypy time during withdrawal appear to last longer than both gene expression and dopamine turnover changes. Tyrosine hydroxylase also displays increased expression during amphetamine withdrawal, while dopamine transporter expression was reduced in specific neuronal cell groups of the ventral tegmental area in animals sacrificed during "withdrawal" from cocaine administration, as noted above.

DDPCR has identified several cDNAs whose sequences are known and several cDNAs different from any other sequence in the GenBank database. Northern analyses of these mRNAs are being pursued to reveal which species are altered in expression with three amphetamine treatment and withdrawal.

Persico AM, Schindler CW, Brannock MT, Gonzalez AM, Surratt CK, Uhl GR. Dopaminergic gene expression during amphetamine withdrawal, NeuroReport 1993;4(1):41-4.

Persico AM, Schindler CW, O'Hara BF, Brannock MT, Uhl GR. Brain transcription factor expression: effects of acute and chronic amphetamine and injection stress, Mol Brain Res 1993;in press.

Miner LL, Pandalai SP, Weisberg EP, Sell SR, Kovacs DM, Kaplan BB. Cold-induced alterations in the binding of adrenomedullary nuclear proteins to the promoter region of the tyrosine hydroxylase gene, J Neurosci Res 1992;10-8.

Baruchin A, Vollmer RR, Miner LL, Sell SL, Stricker EM, Kaplan BB. Cold-induced increases in phenylethanolamine N-methyltransferase (PNMT) mRNA are mediated neurally by a non-cholinergic mechanism in the rat adrenal gland, Neurochem Res 1993;18:759-66..

Miner LL, Baruchin A, Kaplan BB. Trans-synaptic modulation of rat adrenal tyrosine hydroxylase gene expression during cold stress. In: Kvetnansky R, McCarty R, Axelrod J, eds. Stress: neuroendocrine and molecular approaches. New York: Gordon and Breach Scientific Publishers, 1993;in press.

Persico AM, Schindler CW, O'Hara BF, Brannock MT, Uhl GR. Brain transcription factor expression: effects of acute and chronic amphetamine and injection stress, Mol Brain Res 1993;in press.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00088-02 BPGS

PERIOD COVERED

October 1 1992 to September 30 1993

TITLE OF PROJECT

Effects of Acute and Chronic Drug Administration on Gene Expression

PRINCIPAL INVESTIGATOR

P.I.	LL Miner	Senior Staff Fellow	Preclinical Pharmacology Laboratory
	SR Goldberg	Chief	Preclinical Pharmacology Laboratory
	RJ Marley	Senior Staff Fellow	Preclinical Pharmacology Laboratory
	GI Elmer	Staff Fellow	Preclinical Pharmacology Laboratory

COOPERATING UNITS

LAB/BRANCH

Preclinical Pharmacology Laboratory

SECTION

Behavioral Pharmacology

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
0.8	0.8	0

CHECK APPROPRIATE BOXES

☐ (A) Human ☐ (b) Human Tissue ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

Chronic administration of cocaine to rodents results in a progressive enhancement in the drug's motor-stimulating effects. The neurobiological mechanisms that underlie these observed behavioral changes are not well understood. However, the dopaminergic system plays a critical role in the long-term changes that occur after chronic exposure to cocaine. How dopamine exerts its long-term effects is unknown but the discovery that dopaminergic agonists both direct (apomorphine) and indirect (cocaine) induce the expression of a family of genes called immediate early genes (IEGs) may offer new insights. These IEGs, for example, c-fos and c-jun, are known to encode transcriptional activating (or inhibiting) factors that in turn alter the expression of other genes. It is these alterations in gene expression that likely underlie the long term behavioral changes that occur after chronic drug exposure. Pharmacogenetic techniques have proven to be valuable tools for examining the neurochemical mechanisms which underlie and contribute to drug response. However, researchers that have searched for differences in measures such as enzyme and receptor protein levels have met with limited success as far as explaining observed strain differences in more complex, multigenic phenotypes such as response to chronic drug treatment. An individual's response to chronic cocaine exposure is undoubtedly due to changes in a number of neurobiological parameters. Because the IEGs are the link between extracellular signals, such as drug exposure, and long-term adaptive changes that require alterations in gene expression in a number of systems, we have recently begun examining the effects of both acute and chronic cocaine administration on the expression of three IEGs, c-fos, c-jun and zif268, in several inbred strains of mice that have been shown to differ in their initial sensitivity to cocaine. It is possible, first, that there may be strain differences in the expression of these transcription factors that could explain observed strain differences in drug response and/or second, that examination of these transcriptional regulatory pathways may yield insights into which target proteins are being affected by chronic drug exposure.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00089-02 BPGS

PERIOD COVERED

October 1 1992 to September 30 1993

TITLE OF PROJECT

Analysis of the Neural Substrates Mediating the Motivational Effects of Opiates

PRINCIPAL INVESTIGATOR

P.I.	TS Shippenberg	Senior Staff Fellow	Preclinical Pharmacology Laboratory
	SR Goldberg	Chief	Preclinical Pharmacology Laboratory
	C Heidreder	Visiting Fellow	Preclinical Pharmacology Laboratory
	M Shoaib	Visiting Fellow	Preclinical Pharmacology Laboratory

COOPERATING UNITS

LAB/BRANCH

Preclinical Pharmacology Laboratory

SECTION

Behavioral Pharmacology

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
4.9	2.9	2

CHECK APPROPRIATE BOXES

☒ (A) Human ☐ (b) Human Tissue ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

The mesocorticolimbic dopamine (DA) system has been implicated in mediating the rewarding effects of various drugs of abuse. An involvement of this system in the development of drug-induced tolerance, withdrawal and sensitization, phenomenon which are thought to play a role in drug-craving and relapse, has more recently been postulated. Given the apparent involvement of mesolimbic neurons in the addiction process, ongoing studies are seeking to determine: i) whether manipulations which alter mesolimbic neuronal activity can alter the pharmacological and/or neurochemical effects of psychoactive drugs and ii) whether differences in the basal activity of this system or its responsivity to drugs of abuse underlie individual differences in compulsive drug-seeking behavior. Towards that end, classical (place preference conditioning) and operant (drug discrimination, self-administration) conditioning techniques, developed in the past year, are being used to characterize the rewarding effects of opioids and psychostimulants and to determine those pharmacological treatments which lead to or prevent sensitization. In-vivo microdialysis combined with HPLC and electrochemical detection is being used to quantitate dopamine and serotonin release/metabolism within the mesocorticolimbic system in response to various drugs of abuse and to various drug pretreatments. Identical studies in selected inbred rat strains are being initiated and the data generated will permit analysis of the neurochemical substrates underlying vulnerability to drug abuse.

Bals-Kubik R, Ableitner A, Herz A, Shippenberg TS. Neuroanatomical sites mediating the motivational effects of opioids as mapped by the conditioned place preference paradigm in rats. J Pharmacol Exp Ther 1993; 264: 489-495

Heidbreder C, Goldberg SR, Shippenberg TS. The kappa opioid receptor agonist U-69593 attenuates cocaine-induced behavioral sensitization in the rat. Brain Res 1993; 616: 335-338.

Heidbreder C, Goldberg SR, Shippenberg TS. Inhibition of cocaine-induced sensitization by the delta opioid receptor antagonist naltrindole. Eur. J. Pharmacol, in press.

Herz A, Shippenberg TS, and Spanagel R. Analysis of addictive processes: neurotransmitter mechanisms. In: Cohen-Yanez J, Amezcua-Gastelum, Villarreal J, Zavala LS eds., Drug dependence from the molecular to the social level. Elsevier, Amsterdam, 1992; 80-90.

Spanagel R, Almeida OFX, Shippenberg TS. Long-lasting changes in morphine-induced mesolimbic dopamine release after chronic morphine exposure. Synapse, in press.

Shippenberg TS Motivational effects of opioids. In: Herz A, Akil H, Simon E eds. Handbook of Experimental Pharmacology: Opioids II. Springer-Verlag, Heidelberg, 1993; 33-46.

Shippenberg TS, Bals-Kubik R, Herz A. Examination of the neurochemical substrates mediating the motivational effects of opioids: Role of the mesolimbic dopamine system and D-1 vs. D-2 dopamine receptors. J Pharmacol Exp Ther 1993; 265: 53-59

Shippenberg TS, Herz A, Spanagel R, Bals-Kubik R, Stein C. Conditioning of opioid reinforcement: neuroanatomical and neurochemical substrates. In: Kalivas P, Samson S. eds. Neurobiology of drug and alcohol addiction . Ann NYAS 1992; 654: 347-357.

Spanagel R, Almeida OFX, Bartl C, Shippenberg TS. Endogenous kappa opioid systems in opiate withdrawal: role in aversion and accompanying changes in mesolimbic dopamine release. Psychopharmacology, in press:

Spanagel R, Shippenberg TS. Modulation of morphine-induced sensitization by endogenous kappa opioid systems. Neurosci Let 1993; 153: 232-236

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00093-02 BDS

PERIOD COVERED

October 1 1992 to September 30 1993

TITLE OF PROJECT

Pupillometric Studies of Drug Actions

PRINCIPAL INVESTIGATOR

P.I.	WB Pickworth	Pharmacologist	Clinical Pharmacology Branch
	JE Henningfield	Chief	Clinical Pharmacology Branch
	EJ Cone	Chief	Clinical Pharmacology Branch

COOPERATING UNITS

LAB/BRANCH

Clinical Pharmacology Branch

SECTION

Biology of Dependence

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
0.1	0.1	0

CHECK APPROPRIATE BOXES

☒ (A) Human ☐ (b) Human Tissue ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

The effects of drugs on pupillary dynamics and function provide an assessable model for investigating neurophysiologic actions of drugs. For example, animal research at the ARC have utilized pupillary assessment to characterize the neural mechanisms of action of a range of psychomotor stimulants and opioids with affinities for different receptors. This research has been extended to clinical studies where the pupillary effects of several classes of abused drugs were compared to their performance and subjective effects. Additional research on retinal physiology using newly developed pupilometers has yielded new information of the retinal processing of the light reflex. Since retinal neural organization mimics brain neural systems, it is proposed that the influence of drugs in this system indicates drug mechanisms elsewhere in the brain. Dependent measures of these studies include pupil size, constriction and dilation velocities of the light reflex, smooth pursuit and saccadic tracking. These studies are typically within subject repeated measure design, when drugs are administered it is double blind and placebo controlled. Progress to date: The effects of marijuana, ethanol, cocaine, opiates amphetamine have been studies after various routes of administration.

Fosnaugh, J.S. Bunker, E.B., Pickworth, W.B. Daily variation and effects of ambient light and circadian factors on the human light reflex. Meth Find Clin Exp Pharmacol 14:545-553, 1992.

Pickworth, W.B., Johnson, R.E., Holicky, B.A., and Cone, E.J. Subjective and physiologic effects of buprenorphine in humans. Clin Pharmacol Ther 53:570-576, 1993.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00101-08 BPGS

PERIOD COVERED

October 1 1992 to September 30 1993

TITLE OF PROJECT

Pharmacogenetics: Acute Response to Drug Administration

PRINCIPAL INVESTIGATOR

P.I.	GI Elmer	Staff Fellow	Preclinical Pharmacology Laboratory
	SR Goldberg	Chief	Preclinical Pharmacology Laboratory
	TS Shippenberg	Senior Staff Fellow	Preclinical Pharmacology Laboratory
	CW Schindler	Research Psychologist	Preclinical Pharmacology Laboratory
	RR Rothman	Chief	Clinical Pharmacology Branch

COOPERATING UNITS

LAB/BRANCH

Preclinical Pharmacology Laboratory

SECTION

Behavioral Pharmacology

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
3.2	1.2	2

CHECK APPROPRIATE BOXES

☐ (A) Human ☐ (b) Human Tissue ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

The purpose of the current research has been to develop a series of complementary projects using a behavior genetics approach to investigate pharmacological and behavioral factors important in drug abuse. Genetic factors involved in the acute, chronic and reinforcing effects of opioids have been investigated. This effort provides data important for testing pharmacological mechanisms thought to be important in the drug effect. For example, large differences in the potency versus efficacy of morphine-induced analgesia were found to vary independently as a function of genotype. In vivo methods for determining agonist effective receptor reserve, agonist affinity and stimulus-response relationships indicate that receptor reserve and modulation of mu-opioid effects by delta-mechanisms are responsible, in part, for genetic differences in potency and therapeutic efficacy, respectively. In addition, innate nociception as determined by stimulus-effect curves significantly influences the potency of opioid-induced analgesia. The results of these types of studies demonstrate genotype and the use of classic receptor theory to be mutually beneficial for investigating pharmacological constructs important in the behavioral effects of a drug and will be applied to more complex measures of drug effect such as drug-reinforced behavior. To this end, genetic and environmental aspects of vulnerability to drug self-administration behavior have been determined in four inbred rat strains. Genetic factors that influence vulnerabilty are moderately related to innate locomotor behavior and significantly influenced by environmental events in a genotype-dependent manner. Additionally, genetic variations in extinction patterns enable further investigation of multiple aspects of the addiction process. Environmental conditioning studies demonstrate genotype to be an important factor in conditioned drug-like effects and may play a role in drug-seeking behavior. Genotype by environment interactions thought to be important in the complex behavioral effects of a drug have been investigated in tolerance and sensitization paradigms and are designed to complement self-administration studies using unique inbred mouse strains.

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Elmer GI, Mathura CB, Goldberg SR. Genetic factors in conditioned tolerance to the analgesic effects of etonitazene. Pharmacol Biochem Behav 1993;45:251-254

Elmer GI, Pieper JO, Goldberg SR, George FR. Opioid self-administration and its relationship to genetic variation in μ opiate receptors, the analgesic, stimulant and respiratory depressant effects of opioids. Psychopharmacology 1993; in press

Pickens RW, Elmer GI, LaBuda MC, Uhl GR. Vulnerability to substance abuse. In: Schuster CR ed. Handbook of Experimental Pharmacology, Springer-Verlag, Berlin, 1993; in press

Sudakov SK, Goldberg SR, Borisova EV, Surkova LA, Turina IV, Rusakov DJ and Elmer GI. Differences in morphine reinforcement property in two inbred rat strains: Associations with cortical receptors, behavioral activity, analgesia and the cataleptic effects of morphine. Psychopharmacology 1993; in press:

Uhl GR, Elmer GI, LaBuda MC and Pickens RW. Genetic influences in drug abuse. In: Meltzer HY ed. Psychopharmacology: The Fourth Generation of Progress, Raven Press, New York, 1993; in press

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00103-04 BPS

PERIOD COVERED

October 1 1992 to September 30 1993

TITLE OF PROJECT

Basic Mechanisms of Cocaine's Behavioral Effects

PRINCIPAL INVESTIGATOR

P.I.	J Katz	Chief	Preclinical Pharmacology Laboratory
	J Witkin	Research Psychologist	Preclinical Pharmacology Laboratory
	A Newman	Senior Staff Fellow	Preclinical Pharmacology Laboratory
	S Izenwasser	Senior Staff Fellow	Preclinical Pharmacology Laboratory
	P Terry	Visiting Fellow	Preclinical Pharmacology Laboratory

COOPERATING UNITS

LAB/BRANCH

Preclinical Pharmacology Laboratory

SECTION

Psychobiology

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
4	2	2

CHECK APPROPRIATE BOXES

☐ (A) Human ☐ (b) Human Tissue ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

The primary focus of this research is to develop a better understanding of the pharmacological mechanisms underlying the behavioral effects of cocaine that lead to its abuse and the consequences of that abuse. Studies have indicated that: (1) the D1 dopamine receptor appears to be more involved than originally concluded in the subjective behavioral effects of cocaine in the monkey than was indicated in the rat. This was established by studying several D1 dopamine receptor agonists. In addition, there is evidence that non dopaminergic effects may be important components of the pharmacological profile cocaine, and these will be studied further. (2) The D1 dopamine-receptor agonist, SKF 38393, blocked the reinforcing effects of cocaine. This effect occurred at doses that had minimal effects on other behaviors. These results suggest that D1 agonists may be useful treatments against cocaine abuse. (3) Studies have continued on the modulation of the effects of cocaine by various types of agents. In particular, studies have examined the effects of sigma receptor ligands and antagonists of excitatory amino acids. (4) The mechanism of the modulation of the effects of cocaine by sigma receptor ligands has been assessed. It appears that some sigma ligands bind to the dopamine transporter. However, these drugs do not produce behavioral effects like those of cocaine. This may be the mechanism for the antagonism of the psychomotor stimulant effects of cocaine by sigma receptor ligands. (5) Tolerance and sensitization can develop to the behavioral effects of cocaine. The mechanisms for these two effects of repeated cocaine dosing are being studied. (6) The synthetic chemistry component of the laboratory has synthesized pyrolysis products of cocaine that have been identified in crack-cocaine users. These compounds do not have cocaine-like effects but do have some structural similarities to known cholinergic toxins. The pharmacology of these compounds is being characterized. (7) Dopamine uptake inhibitors have been synthesized that do not have behavioral effects like those of cocaine. The pharmacology of these drugs is being studied to provide structure-activity relations that will provide basic information on the functioning of the dopamine transporter.

Izenwasser, S.; Newman, A. H.; Katz, J. L., Cocaine and sigma ligands inhibit dopamine uptake via a common low affinity site in the rat caudate putamen. Eur. J. Pharmacol., 1993, in press.

Izenwasser, S., Rosenberger, J.G. and Cox, B.M. The cocaine analog WIN 35,428 binds to two sites in fresh rat caudate putamen under the correct assay conditions. Life Sciences/Pharmacology Letters, 52:PL141 145, 1993.

Unterwald, E.M., Cox, B.M., Kreek, M.J., Cote, T.E. and Izenwasser, S. Chronic repeated cocaine administration alters basal and opioid regulated adenylyl cyclase activity. Synapse, 1993, in press.

Cote, T.E., Izenwasser, S. and Weems, H.B. Naltrexone induced upregulation of μ opioid receptors on 7315c cell and brain membranes: enhancement of opioid efficacy in inhibiting adenylyl cyclase. J. Pharmacol. Exp. Ther., in press.

Izenwasser, S. Buzas, B. and Cox, B.M. Differential regulation of adenylyl cyclase activity by mu and delta opioids in rat caudate putamen and nucleus accumbens. J. Pharmacol. Exp. Ther., in press.

Katz, J. L., Griffiths, J. W., Sharpe, L. G., de Souza, E. B., and Witkin, J. M. Cocaine tolerance and cross tolerance. Journal of Pharmacology and Experimental Therapeutics 264: 183-192, 1993.

Witkin, J. M. Pharmacotherapy of cocaine abuse: Preclinical development. Neuroscience and Biobehavioral Reviews, in press.

Witkin, J. M., Newman, A. H., Nowak, G., and Katz, J. L. Role of dopamine D1 receptors in the lethal effects of cocaine and a quaternary methiodide analog. Journal of Pharmacology and Experimental Therapeutics, in press, 1993.

French, D. and Witkin, J. M. Effects of the dopamine release inhibitor, CGS 10746B, on the locomotor stimulant and discriminative stimulus effects of cocaine and methamphetamine. Pharmacology Biochemistry and Behavior, in press.

Witkin, J.M., Terry, P., Menkel, M., Hickey, P., Pontecorvo, M., Ferkany, J. and Katz, J.L. Effects of the selective sigma receptor ligand, 6-[6-(4-hydroxypiperidinyl)hexyloxy]-3-methylflavone (NPC 16377), on behavioral and toxic effects of cocaine. Journal of Pharmacology and Experimental Therapeutics, 266: 473-482, 1993.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00104-04 BPS

PERIOD COVERED

October 1 1992 to September 30 1993

TITLE OF PROJECT

Drug Development

PRINCIPAL INVESTIGATOR

P.I.	J Witkin	Research Psychologist	Preclinical Pharmacology Laboratory
	J Katz	Chief	Preclinical Pharmacology Laboratory
	A Newman	Senior Staff Fellow	Preclinical Pharmacology Laboratory
	A Allen	Guest Worker	Preclinical Pharmacology Laboratory
	J Shah	IRTA	Preclinical Pharmacology Laboratory

COOPERATING UNITS

LAB/BRANCH

Preclinical Pharmacology Laboratory

SECTION

Psychobiology

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
4	3	1

CHECK APPROPRIATE BOXES

☐ (A) Human ☐ (b) Human Tissue ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

These studies are designed to provide preclinical information for the development of medications to be used in the treatment of drug abuse. The primary focus of this work is to determine pharmacological means for modulating behavioral and toxic actions of abused compounds, and to evaluate new chemical entities (synthesized in house and from outside sources) for safety and efficacy in the design of potential rational treatment strategies.

The primary findings and implications for the current year are: (1) Certain sigma-receptor ligands have shown an ability to antagonize some of the pharmacological effects of cocaine. We are examining other sigma ligands to determine which ones are most effective as antagonists of cocaine and to determine the mechanisms of this effect. Ongoing studies will determine whether other behavioral effects of cocaine related to its abuse and toxicity can be similarly altered. (2) A variety of compounds proposed by NIDA as potential treatments for cocaine abuse are being examined in preclinical screens for safety and efficacy as potential treatments for cocaine abuse. (3) Studies have indicated that the locomotor stimulant effects of cocaine can be modulated by several excitatory amino acid antagonists. These drugs are being characterized and various other effects of cocaine, such as the toxic, subjective and reinforcing effects, will be examined as indicated as further results unfold. (4) Studies of the lethal effects of cocaine have indicated a significant peripheral D1 component to the mediation of these effects. We have synthesized several peripherally active D1 antagonists and will be testing them for their effectiveness in protecting against the lethal effects of cocaine. (5) The synthetic chemistry component of the laboratory is developing novel compounds as potential treatments against cocaine abuse.

Izenwasser, S.; Newman, A. H.; Katz, J. L., Cocaine and sigma ligands inhibit dopamine uptake via a common low affinity site in the rat caudate putamen. Eur. J. Pharmacol., 1993, in press.

Witkin, J. M. Pharmacotherapy of cocaine abuse: Preclinical development. Neuroscience and Biobehavioral Reviews, in press.

Wong, G., Skolnick, P., Katz, J. L. and Witkin, J. M. Transduction of a discriminative stimulus through a diazepam-insensitive GABAA receptor. Journal of Pharmacology and Experimental Therapeutics 266: 570-576, 1993.

Witkin, J. M., Newman, A. H., Nowak, G., and Katz, J. L. Role of dopamine D1 receptors in the lethal effects of cocaine and a quaternary methiodide analog. Journal of Pharmacology and Experimental Therapeutics, in press, 1993.

French, D. and Witkin, J. M. Effects of the dopamine release inhibitor, CGS 10746B, on the locomotor stimulant and discriminative stimulus effects of cocaine and methamphetamine. Pharmacology Biochemistry and Behavior, in press.

Witkin, J.M., Terry, P., Menkel, M., Hickey, P., Pontecorvo, M., Ferkany, J. and Katz, J.L. Effects of the selective sigma receptor ligand, 6-[6-(4-hydroxypiperidinyl)hexyloxy]-3-methylflavone (NPC 16377), on behavioral and toxic effects of cocaine. Journal of Pharmacology and Experimental Therapeutics, 266: 473-482, 1993.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00105-04 BPS

PERIOD COVERED

October 1 1992 to September 30 1993

TITLE OF PROJECT

Behavioral Pharmacology of Dopamine Systems

PRINCIPAL INVESTIGATOR

P.I.	J Katz	Chief	Preclinical Pharmacology Laboratory
	J Witkin	Research Psychologist	Preclinical Pharmacology Laboratory
	S Izenwasser	Senior Staff Fellow	Preclinical Pharmacology Laboratory
	P Terry	Visiting Fellow	Preclinical Pharmacology Laboratory
	A Newman	Senior Staff Fellow	Preclinical Pharmacology Laboratory

COOPERATING UNITS

LAB/BRANCH

Preclinical Pharmacology Laboratory

SECTION

Psychobiology

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
3	2	1

CHECK APPROPRIATE BOXES

☐ (A) Human ☐ (b) Human Tissue ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

Studies have been conducted to better document the behavioral pharmacology of drugs acting on dopaminergic systems. These studies have examined specific D1, D2, and D3 dopamine receptor agonists and antagonists. The overall goal of these studies is to better characterize the behavioral pharmacology of drugs acting on these systems and the mechanisms responsible for those behavioral effects. These studies indicate that: (1) some of the D2 agonists can stimulate behavior in a manner similar to cocaine, suggesting that the stimulant effects of cocaine are due to actions mediated through D2 receptors. However, some of the D2 agonists do not have effects that are equivalent to cocaine. An in vitro assay of intrinsic efficacy is being established in order to determine if the differences among these drugs are due to differences in intrinsic efficacy. There currently are no assays available to provide that information. (2) the D1 agonist, SKF 38393, is not well antagonized by D1 antagonists, whereas other D1 agonists are. These results indicate that much of the behavioral effects often attributed to D1 agonist activity of SKF 38393 are likely a result of activation of other mechanisms. Several biochemical studies are being initiated to better understand the actions of D1 agonsits. (3) D2 agonists produce a unique scratching behavior in primates. This effect of these agonists appears to be pharmacologically specific (drugs acting by other mechanisms generally do not produce this effect). Recently, we observed that the D3 agonist, 7-OH-DPAT, also produces this effect, and experiments are being conducted to determine whether the effect of 7-OH-DPAT is being mediated by D2 or D3 receptors. This effect could serve as a good in vivo assay of D2 receptor activity and will be useful in documenting the D2 agonist activity of novel compounds. In addition, it may be used to characterize the D2 agonist sensitivity of primates with various exposures to cocaine, or those that may be acutely sensitive to the effects of drugs of abuse. (4) Biochemical studies have indicated that the D1 receptor in rodents and primates may be significantly different. These results suggest that there has been a phylogeny of the D1 receptor, and that the effects of drugs acting at this receptor in man may not be predictable from studies in rodents.

Tirelli, E. and Terry, P. (1993): Biphasic locomotor effects of the dopamine D-1 agonist SKF 38393 and their antagonism in non-habituated mice. Psychopharmacology, 110:69-75.

Izenwasser, S. and Katz, J.L. Differential efficacies of dopamine D1 receptor agonists for stimulating adenylyl cyclase activity in squirrel monkey and rat. Eur. J. Pharmacol. Mol. Pharmacol. Sect., 246:39 44, 1993.

Katz, J. L. and Witkin, J. M. Behavioral effects of dopaminergic agonists and antagonists alone and in combination in the squirrel monkey. Psychopharmacology, in press.

Terry, P. and Katz, J.L. A comparison of the effects of D-1 receptor antagonists SCH 23390 and SCH 39166 on suppression of feeding behavior by the D-1 agonist SKF 38393. Psychopharmacology, 00: 00-00, 1993.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00107-08 MPS

PERIOD COVERED

October 1 1992 to September 30 1993

TITLE OF PROJECT

Drug Receptors in Vivo: Animal Models and Imaging

PRINCIPAL INVESTIGATOR

P.I.	MJ Kuhar	Chief	Neuroscience Branch
	J Boja	Senior Staff Fellow	Neuroscience Branch
	E Cline	PRAT Fellow	Neuroscience Branch
	E Shaya	Staff Fellow	Neuroscience Branch

COOPERATING UNITS

FI Carroll, Research Triangle Institute

LAB/BRANCH

Neuroscience Branch

SECTION

Molecular Pharmacology

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
2	1.5	0.5

CHECK APPROPRIATE BOXES

☐ (A) Human ☐ (b) Human Tissue ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

While most receptors are studied by binding techniques in in vitro experiments, it is obviously important to carry out similar studies in vivo where receptors function normally. One of our goals is to study drug receptors related to addiction in vivo by ligand binding and imaging techniques. In the procedure of in vivo labeling, radioactive ligands are injected systemically into animals such that the ligands preferentially localize to drug receptor sites. In our structure-activity studies of the cocaine receptor with cocaine analogs, we found that RTI-55 was a very potent compound with high affinity for the dopamine transporter. Experiments carried out in vivo shows that RTI-55 can indeed bind to dopamine transporters in vivo. It accumulates in brain regions having high densities of transporter such as the striatum, accumulation in these regions are blocked by drugs which bind to the transporter and lesions of these dopaminergic nerve terminals result in a reduced accumulation in these regions.

However, ligands such as RTI-55, while they are useful imaging agents, are not selective for the dopamine transporter. For example, RTI-55 also binds with a relatively high affinity to the serotonin transporter. It is highly desirable that very selective binding compounds be generated. Accordingly, we have developed a number of compounds which are selective for the dopamine transporter. One of these compounds, RTI-121, is especially promising and will probably replace RTI-55 as an in vitro binding ligand and perhaps as an in vivo binding ligand as well. We have also made significant progress in further developing older, more established compounds. We have utilized carbon-11 labeled WIN 35,428 as a PET scanning ligand and have carried out preliminary modeling studies as well as pharmacological studies. The results clearly indicate that the compound can be used effectively to localize dopamine transporters in human populations by PET scanning. In summary, we have made significant progress in identifying and developing binding ligands which will allow us to study drug receptors in vivo.

Cline EJ, Scheffel U, Boja JW, Mitchell WM, Carroll FI, Abraham P, Lewin AH and Kuhar MJ. In vivo Binding of [125I]RTI-55 to Dopamine Transporters: Pharmacology and Regional Distribution with Autoradiography. Synapse 12, 37-46, 1992.

Scheffel U, Dannals RF, Wong DF, Yokoi F, Carroll FI and Kuhar MJ. Dopamine Transporter Imaging with Novel, Selective Cocaine Analogs. Neuroreport 3: 969-972, 1992.

Kuhar MJ and DeSouza EB. Receptor Autoradiography as an Aid in Explaining Drug Action. In: Imaging Drug Action in the Brain. E.D. London (Ed.), CRC Press. pp. 49-60, 1993.

Wong DF, Yung B, Dannals R.F., Shaya EK, Ravert HT, Chen CA, Chan B, Folio T, Scheffel U, Ricaurte GA, Neumeyer JL, Wagner HN, Jr. and Kuhar MJ. In Vivo Imaging of Baboon and Human Dopamine Transporters by Positron Emission Tomography Using [11C]WIN 35,428. Synapse, in press.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00108-06 MPS

PERIOD COVERED

October 1 1992 to September 30 1993

TITLE OF PROJECT

The Cocaine Receptor: Structure Activity Relationships and Ligand Binding Studies

PRINCIPAL INVESTIGATOR

PI.	MJ Kuhar	Branch Chief	Neuroscience Branch
	I Carroll		Research Triangle Institute
	J Boja	Senior Staff Fellow	Neuroscience Branch
	A Patel	Staff Fellow	Neuroscience Branch

COOPERATING UNITS

Research Triangle Institute

LAB/BRANCH

Neuroscience Branch

SECTION

Molecular Pharmacology

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER
4	2	2

CHECK APPROPRIATE BOXES

☐ (A) Human ☐ (b) Human Tissue ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

The goal of this project is to carry out a detailed structure-activity study for purposes of understanding the interaction of cocaine with its receptor sites in brain. The receptor thought important for the reinforcing effects of cocaine is the dopamine transporter and other effects of the drug are likely to be due to interaction at other sites such as other transporters. Also, knowledge gained for this study will be used to design potent reversible and irreversible binding ligands for transporters.

Previous work showed that large changes in activity were created when modifications were made in different parts of the cocaine molecule. A major modification was the elimination of the ester link between the phenyl group and the tropane moiety at C-3. The elimination of this group resulted in a series of highly potent compounds. One of these compounds, RTI-55, had a very high affinity for the dopamine transporter. It was found that the compound had a high affinity for dopamine transporters but also was bound by serotonin transporters. The high affinity of this compound indicated that it was probably useful for in vivo binding studies.

Our structure-activity work also suggested that modification of the ester group at C-2 greatly altered the selectivity of the compounds for the various transporters. We accordingly carried out a systematic study and showed that isopropyl and phenyl substitutions provided compounds among the most selective for the dopamine transporter. Some of these compounds are currently being evaluated as binding ligands and in behavior of animals. These compounds can be utilized to selectively explore the effects of cocaine at the dopamine transporter while leaving out effects at other transporters.

We also prepared a series of compounds where oxadiazoles were utilized in the C-2 position, as this compound resembles an ester. As expected, many potent compounds were found with varying selectivity. This series is currently being explored in more detail.

Boja, J.W., E.J. Cline, F.I. Carroll, A.H. Lewin, A. Philip, R. Dannals, D. Wong, U. Scheffel, and M.J. Kuhar. High potency cocaine analogs: Neurochemical, imaging, and behavioral studies. Annals of the New York Acad. of Sci. 654, 282-291, 1992.

Boja, J.W., W.M. Mitchell, A. Patel, T.A. Kopajtic, F.I. Carroll, A.H. Lewin, P. Abraham, and M.J. Kuhar. High-affinity binding of [125I]RTI-55 to dopamine and serotonin transporters in rat brain. Synapse 12, 27-36, 1992.

Boja, J.W., R.M. McNeill, A.H. Lewin, P. Abraham, F.I. Carroll, and M.J. Kuhar. Selective dopamine transporter inhibition by cocaine analogs. Neuroreport 3, 984-986, 1992.

Carroll, F.I., J.L. Gray, P. Abraham, M.A. Kuzemko, A.H. Lewin, J.W. Boja, and M.J. Kuhar. 3-Aryl-2-(3'-Substituted-1',2'4'-oxadiazole-5'yl)tropane analogues of cocaine: Affinities at the cocaine binding site at the dopamine, serotonin, and norepinephrine transporters. J. Med. Chem. in press.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00112-07 MPS

PERIOD COVERED

October 1 1992 to September 30 1993

TITLE OF PROJECT

Drug Receptors, Neurotransmitters and Addiction

PRINCIPAL INVESTIGATOR

P.I.	MJ Kuhar	Branch Chief	Neuroscience Branch
	FI Carroll		Research Triangle Institute
	J Boja	Senior Staff Fellow	Neuroscience Branch
	N Pilotte	Staff Fellow	Neuroscience Branch
	C Cerruti	Visiting Fellow	Neuroscience Branch

COOPERATING UNITS

Research Triangle Institute

LAB/BRANCH

Neuroscience Branch

SECTION

Molecular Pharmacology

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
2	1.5	0.5

CHECK APPROPRIATE BOXES

☐ (A) Human ☐ (b) Human Tissue ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

The focus of this project is to elucidate mechanisms involved in the repetitive use of drugs, the long-term effects of drugs and the biochemical mechanisms underlying chronic drug taking and drug seeking behavior. In a series of studies, we treated animals with cocaine in a long-term, but intermittent fashion. The pattern of administration was similar to that observed in animals self-administering cocaine. We utilized Lewis rats as they show a propensity for self administering cocaine compared to other strains. We found that, after 10 days of withdrawal, there was a significant decrease in dopamine transporter (a cocaine receptor) binding in the nucleus accumbens but not in the striatum. The decrease in transporter binding in the accumbens was long-lasting and still apparent by 60 days after withdrawal. Thus, there is a long-lasting change in dopamine transporter in limbic areas which appears during the withdrawal period and which is persistent. This type of biochemical phenomena could be related to long-term effects of drugs in human populations.

In an effort to elucidate the mechanism of this down regulation of transporter, we carried out an in situ hybridization study in collaboration with Dr. George Uhl. We found a significant reduction in dopamine transporter mRNA in midbrain cell groups that project to the nucleus accumbens. Changes in mRNA were not found in cell groups projecting to the striatum. These data indicate that changes in gene expression can occur during drug withdrawal and also that regulation of the dopamine transporter can involve a change in gene expression.

Taken together, we have carried out a series of successful studies in changes in the dopamine transporter during chronic drug administration and withdrawal.

Rostene W, Boja JW, Scherman D, Carroll FI, Kuhar MJ Dopamine transport: pharmacological distinction between the synaptic membrane and the vesicular transporter in rat striatum. Eur. J. Pharmacol. 1992;218:175-177.

Pilotte NS, Sharpe LG and Kuhar MJ. Withdrawal of repeated intermittent intravenous infusions of cocaine results in the delayed recuction of binding to dopamine transporters in the nucleus accumbens of Lewis Rats. JPET 1993 in press.

Cerruti C, Pilotte NS, Uhl GR and Kuhar MJ. Reduction in dopamine transporter mRNA after cessation of repeated cocaine administration. Brain Research 1993, in press.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00118-02 CDM

PERIOD COVERED

October 1 1992 to September 30 1993

TITLE OF PROJECT

Pharmacodynamics of Smoked Drugs of Abuse

PRINCIPAL INVESTIGATOR

P.I.	EJ Cone	Chief	Clinical Pharmacology Branch
	WD Darwin	Chemist	Clinical Pharmacology Branch
	A Jenkins	Staff Fellow	Clinical Pharmacology Branch
	D Yousfnejad	Chemist	Clinical Pharmacology Branch

COOPERATING UNITS

LAB/BRANCH

Clinical Pharmacology Branch

SECTION

Chemistry

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
0.9	0.1	0.8

CHECK APPROPRIATE BOXES

☒ (A) Human ☐ (b) Human Tissue ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

The smoking route is an efficient means of drug delivery. Numerous drugs of abuse are administered by this route including cocaine, marijuana, phencyclidine, heroin and methamphetamine. Methods were developed to study the pharmacokinetics and pharmacodynamics of smoked drugs of abuse in human volunteer subjects. Healthy subjects with a recent history of abuse of the drug of interest by the smoking route participated in the studies. Following informed consent, the subjects smoked a low dose of the drug under controlled conditions to assess safety of the procedures. The subjects then participated in a double blind, placebo controlled study of smoked versus intravenous administration of drug. Behavioral and physiological measures and biological samples were collected over time. These data provide important information to our understanding of the pharmacologic actions of these drugs by the smoking route.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00119-02 CPS

PERIOD COVERED

October 1 1992 to September 30 1993

TITLE OF PROJECT

Mechanisms of Action of Cocaine

PRINCIPAL INVESTIGATOR

PI	RB Rothman	Section Chief	Clinical Pharmacology Branch
	JL Cadet	Senior Staff Fellow	Clinical Pharmacology Branch
	DA Gorelick	Branch CHief	Treatment Branch
	S Goldberg	Branch Chief	Preclinical Pharmacology Laboratory
	J Henningfield	Branch Chief	Clinical Pharmacology Branch

COOPERATING UNITS

KC Rice, J Glowa Lab of Medicinal Chem, NIDDK
A Pert, BPB, NIMH
FI Carroll, RTI

LAB/BRANCH

Clinical Pharmacology Branch

SECTION

Clinical Psychopharmacology

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER
3	2	1

CHECK APPROPRIATE BOXES

☒ (A) Human ☐ (b) Human Tissue ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

The Clinical Psychopharmacology Section conducts preclinical and clinical research into the mechanisms of action of cocaine. A major component of this project, conducted in collaboration with investigators at NIDDK and NIMH, is the synthesis and evaluation of analogs of GBR12909 as putative cocaine antagonists. This project has identified several promising novel agents, including the most selective dopamine uptake inhibitor reported. Other studies show that GBR12909 suppresses cocaine self-administration in Rhesus monkeys, supporting its potential use in the treatment of cocaine addiction and blocks the cocaine-induced increase in extracellular DA as measured by in vivo microdialysis. Another componentinvolves investigation of the possible heterogeneity of DA transporter binding sites. This project has identified three binding sites for the DA transporter ligands [3H]GBR12935, [3H]BTCP, and a single binding site for [3H]mazindol. Another component of this project addresses the role of classical conditioning in cocaine-induced behavioral sensitization. These studies demonstrated that associative learning mechanisms are involved in the acquisition of context-specific behavioral sensitization to cocaine. Studies with genetically inbred strains of mice showed that the occurrence of sensitization is not correlated with either the potency or efficacy of cocaine as a motoric stimulant. Preliminary human studies failed to demonstrate cocaine-sensitization with a one day training paradigm (ARC-174). Clinical protocols, currently underway, 1) test the DA hypothesis of cocaine addiction by acute administration of cocaine to subjects who are on various DA receptor antagonists (ARC-170); and 2) attempt to develop a human model of context-specific behavioral sensitization to cocaine (ARC-174). The significance of these findings to drug abuse research is that increased understanding of how cocaine works will lead to the development of improved treatments.

Akunne, H. C., B. R. de Costa, K. C. Rice and R. B. Rothman (1992). Evidence for multiple [3H]GBR12935 binding sites associated with the dopaminetransporter inrat striatal membranes. NIDA Research Monograph 119:237.

Aulakh CH, Kilburn R, de Costa BR, Rice KC, Rothman RB. Chronic administration of GBR12909 partially attenuates cocaine-induced locomotor activity in rats, NIDA Research Monograph 1992; 119:403.

Rothman RB, Kim A, Greig N, de Costa BR, Rice KC, Carroll FI, Pert A.Preliminary evidence that GBR12909 is less effective at elevating mesolimbic dopamine function than cocaine, NIDA Research Monograph 1992;119:338.

Rothman RB, Greig N, Kim A, de Costa BR, Rice KC, Carroll FI, Pert A. Cocaine and GBR12909 produce equivalent motoric responses at different occupancy of the dopamine transporter. Pharmacol. Biochem. Behav. 1992; 43:1135-1142.

Akunne HC, Dersch C, Char GU, Partilla JS, de Costa BR, Rice KC, Rothman RB.Resolution of multiple [3H]GBR12935 and [3H]BTCP binding sites in rat striatal membranes, NIDA Research Monograph 1993; 132:105.

Rothman RB, Pert A. Electroconvulsive shock prevents cocaine-induced conditioning, NIDA Research Monograph 1993; 132:233

Matecka DL, Radesca L, de Costa B, Rothman RB, Dersch C, Akunne H, Lewis B,Partilla J, Xu H, Pert A, Rice KC. Synthesis, receptor binding and behavioral studies of N-(2-diphenylmethoxyethyl)-N-(3-henylpropyl)HOMOPIPERAZINE, (a Novel GBR12935 Analog), NIDA Research Monograph 1993; 132:381.

Baumann MH, Raley TJ, Partilla JS, Rothman RB. Dopamine and serotonin biosynthesis in rat brain after chronic cocaine, NIDA ResearchMonograph 1993; 132:398.

Dersch C, Akunne HC, Partilla JS, Char GU, de Costa BR, Rice KC Rothman RB. A study on the mechanism by which dopamine reuptake blockers inhibit [3H]mazindol binding to the dopamine transporter, NIDA Research Monograph 1993; 132:399.

Baumann MH, Rothman RB. Effects of acute and chronic cocaine on the activity of tuberoinfundibular dopamine neurons in the rat, Brain Research 1993;608:175-179.

Baumann MH, Raley TJ, Partilla JS, Rothman RB. Biosynthesis of dopamine and serotonin in rat brain after repeated cocaine injections: a microdissection mapping study, Synapse 1993; 14:40-50.

Rothman RB, Lewis B, Dersch C, Xu H, Radesca L, de Costa BR, Rice KC, Kilburn RB, Akunne HC, Pert A. Identification of a GBR12935 Homolog, LR1111, which is over 4000-fold selective for the dopamine transporter, relative to serotonin and norepinephrine transporters, Synapse 1993; 14:34-39.

Dersch CM, Akunne HC, Partilla JS, Char GU, de Costa BR, Rice KC, Carroll FI, Rothman RB. Studies of the biogenic amine transporters. I. dopamine reuptake blockers inhibit [3H]mazindol binding to the dopamine transporter by a competitive mechanism: preliminary evidence for different binding domains, Neurochemical Research, 1993; in press.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00120-02 CPS

PERIOD COVERED

October 1 1992 to September 30 1993

TITLE OF PROJECT

Characterization of Anti-Opioid Peptides in Opioid Tolerance to Dependence

PRINCIPAL INVESTIGATOR

P.I.	RB Rothman	Section Chief	Clinical Pharmacology Branch
	H Xu	Visiting Scientist	Clinical Pharmacology Branch
	C Goodman	IRTA	Clinical Pharmacology Branch
	M Bauman	Staff Fellow	Clinical Pharmacology Branch
	JL Cadet	Senior Staff Fellow	Clinical Pharmacology Branch

COOPERATING UNITS

LAB/BRANCH

Clinical Pharmacology Branch

SECTION

Clinical Psychopharmacology

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
3	2	1

CHECK APPROPRIATE BOXES

☒ (A) Human ☒ (b) Human Tissue ☐ (c) Neither

☐ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK

The CNS synthesizes and secretes several neuropeptides which attenuate the actions of morphine including CCK-8, Tyr-MIF, Phe-Leu-Phe-Gln-Pro-Gln-Arg-Phe-NH2 (NPFF), alpha-MSH and dynorphin(1-17). The anti-opioid model of tolerance and dependence postulates that administration of morphine produces increased secretion of anti-opioids, which attenuate the effects of morphine, and thereby maintain a homeostatic balance. A prediction of the anti-opioid model is that administration of an anti-opioid should attenuate the development of tolerance and dependence. A major finding of this project is that administration of anti-NPFF IgG to dependent rats attenuates naloxone-induced withdrawal. In addition, other studies have shown that the density of the opioid mu receptor is under tonic inhibitory control by NPFF. Heroin addicts suffer from dysphoric mood states prior to and during their addiction, as well as during periods of abstinence. One hypothesis to explain this is increased levels of dynorphin, which, via activation of kappa opioid receptors, produces dysphoria. This hypothesis is being tested in various ways by two approved protocols: 1) The effect of buprenorphine on dysphoria produced by high-dose naloxone in non-dependent opiate-abusing humans (ARC-184) which has been on-hold for 1992-1993 and 2) Anti-opioid peptide levels in the plasma and CSF of drug abusers and age matched controls (ARC-192). We have begun the process, in a CRADA with Eli Lilly Corp., the process of developing kappa-selective antagonists with which to determine the role of kappa opioid receptors in opioid tolerance and dependence. The significance of this project to drug abuse research is that the delineation of novel mechanisms involved in opioid tolerance and dependence will eventually lead to novel, and more specific treatments for addiction.

Rothman, RB, Xu H, Yang H-YT, Long JB. Anti-opioid peptides in morphine tolerance and dependence: focus on NPFF. In: Neurobiology of Opiates, CRC Press, Inc., R. Hammer, Ed, 1993; p.p. 147-163.

Rothman RB. A review of the role of anti-opioid peptides in morphine tolerance and dependence, Synapse 1992; 12:129-138.

Raffa RB, Kim A, Rice KC, de Costa BR, Rothman RB. Low Affinity of FMRFamide and four FaRPs (FMRFamide-related peptides), including the mammalian-derived FaRPs F-8-Famide (NPFF) and A-18-Famide, for opioid mu, delta, kappa1, kappa2a or kappa2b receptors, Peptides, 1993; in press.

Rothman RB, Brady LS, Xu H, Long JB. Chronic Intracerebroventricular Infusion of the Anti-Opioid Peptide, Phe-Leu-Phe-Gln-Pro-Gln-Arg-Phe-NH2(NPFF), Down-Regulates Mu Opioid Binding Sites in Rat Brain, Peptides, 1993; in press.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00121-03 CPS

PERIOD COVERED

October 1 1992 to September 30 1993

TITLE OF PROJECT

Structure and Function of Opioid Receptor/Endorphin System

PRINCIPAL INVESTIGATOR

P.I.	RB Rothman	Section Chief	Clinical Pharmacology Branch
	H Xu	Visiting Scientist	Clinical Pharmacology Branch
	Q Ni	Visiting Fellow	Clinical Pharmacology Branch
	Y Cha	Visiting Fellow	Clinical Pharmacology Branch

COOPERATING UNITS

KC Rice, BR de Costa ,LMC, NIDDK
FI Carroll, G Brine, RTI
EA Jones, LDS, NIDDK

LAB/BRANCH

Clinical Pharmacology Branch

SECTION

Clinical Psychopharmacology

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
3	2	1

CHECK APPROPRIATE BOXES

☒ (A) Human ☒ (b) Human Tissue ☐ (c) Neither

☐ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK

The unambiguous demonstration of opioid receptor types, and their endogenous ligands, the endorphins, together with a diverse range of synthetic ligands, has created exciting opportunities for research highly relevant to drug abuse. A major objective of this project is to continue the process of defining new opioid receptor subtypes. This process is optimally accomplished by synergistic collaborations with medicinal chemists to develop (a) selective high affinity ligands for each subtype (b) irreversible ligands with receptor subtype specificity and (c) enantiomeric pairs of these ligands for detection of receptor mediated effects. delta receptor antagonists attenuate alcohol consumption and block morphine tolerance and dependence. The CPS is a leading lab in the determination of delta receptor subtypes.: recent studies demonstrated two subtypes of the delta-ncx binding site, and provided new information about subtypes of the delta-cx subtype. The determination of delta receptor subtypes may lead to new medicines for the treatment of alcoholism and drug addiction. Converging lines of investigation suggest that kappa receptor antagonists may be useful for the treatment of depression, anxiety, psychosis and craving. Studies reported last year demonstrated up to four subtypes of kappa opioid receptors in rat, guinea pig and human brain, suggesting that it may be possible to develop kappa agonists devoid of psychotomimetic side effects. More recent studies have resolved yet more kappa receptor subtypes.

Investigations carried out with highly potent analogs of (+)-cis-3-methylfentanyl have identified analogs over 100,000 x the antinociceptive potency of morphine and allowed us to determine the stereochemical requirements of pseudoirreversible inhibition. These drugs provide unique information about the topography of the mu receptor binding site, and interact with the mu receptor according to a pseudoallosteric mechanism. The notion that dysfunction of the CNS opioid receptor/endorphin system underlies certain mental illnesses, and contributes to drug abuse, remains a viable, but unproved. hypotheses. Recent work conducted in collaboration with researchers of the Liver Disease Section, NIDDK, provided strong evidence that the opioid receptor/ endorphin system plays an important role in the pathogenesis of choleostatic liver disease. These data will provide a useful model system for studying the more complex phenomena associated with substance abuse.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00122-02 CPS

PERIOD COVERED

October 1 1992 to September 30 1993

TITLE OF PROJECT

Characterization of PCP and Sigma Receptors

PRINCIPAL INVESTIGATOR

P.I.	RB Rothman	Section Chief	Clinical Pharmacology Branch
	C Goodman	IRTA	Clinical Pharmacology Branch
	KC Rice	Lab Chief	LMC, NIDDK
	RB de Costa	Senior Staff Fellow	LMC, NIDDK
	FI Carroll	Chemist	RTI

COOPERATING UNITS

LAB/BRANCH

Clinical Pharmacology Branch

SECTION

Clinical Psychopharmacology

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
3	2	1

CHECK APPROPRIATE BOXES

☐ (A) Human ☐ (b) Human Tissue ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

Phencyclidine (PCP) and sigma receptors, though linked in terms of their historical development, and their generally high affinity interactions with (+)-opiates, are now known to be pharmacologically and biochemically distinct binding sites. The PCP binding site, because it is but one component of the NMDA receptor, is relevant to drug abuse research because the NMDA receptor plays important roles in neuronal processes involved in substance abuse, such as memory, propagation of seizures and kindling, tolerance and dependence. Previous studies showed that the PCP analog, [3H]TCP labels two high affinity PCP binding sites: PCP site 1 (NMDA-receptor-associated) and PCP site 2 (biogenic-amine - transporter-associated). Collaborative investigations with F. Ivy Carroll lead to the discovery of RTI-4793-14, which has high potency and selectivity for PCP site 2. This novel pyrole has a neurochemical profile consistent with that of an antidepressant. A patent application on this compound was filed.

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dopamine transporter, relative to serotonin and norepinephrine transporters. Synapse 14:34-39.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00200-08 NDAS

PERIOD COVERED

October 1 1992 to September 30 1993

TITLE OF PROJECT

Cerebral Effects of Abused Drugs: Brain Imaging Studies

PRINCIPAL INVESTIGATOR

P.I.	ED London	Chief	Neuroscience Branch
	RL Phillips	Senior Staff Fellow	Neuroscience Branch
	JM Stapleton	Research Psychologist	Neuroscience Branch
	SF Gilson	IRTA	Neuroscience Branch
	L Xiang	Visiting Fellow	Neuroscience Branch

COOPERATING UNITS

JE Henningfield, Clinical Pharmacology Branch

LAB/BRANCH

Neuroscience Branch

SECTION

Neuroimaging and Drug Action

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
5.35	4.8	0.55

CHECK APPROPRIATE BOXES

☒ (A) Human ☐ (b) Human Tissue ☐ (c) Neither

☐ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK

@Brain imaging is used to study cerebral metabolic, electrophysiological and structural correlates of drug abuse. Efforts in technical development have yielded an improved form of a conventional model for calculation of cerebral metabolic rate(s) for glucose (CMRglc). The new model allows quantitative analysis of PET data without the need for arterial blood sampling and without the need for collecting blood samples during the early phase of the procedure. Positron emission tomography (PET) and electroencephalography (EEG) of human subjects show that euphoriants reduce global and regional CMRglc, and increase alpha power. The changes in CMRglc and EEG alpha power are correlated with self reports of feeling good, as measured by a subscale of the Addiction Research Center Inventory. Buprenorphine, a mixed opioid agonist, decreases regional CMRglc (rCMRglc) similar to effects produced by morphine and cocaine. Likewise, nicotine decreases rCMRglc; however, the decreases are greater in smokers than in non-smokers, consistent with magnitudes of euphorigenic effects of nicotine in the two populations. As part of a clinical trial designed to test the effectiveness of peptide T on AIDS dementia, the correlation of the effect of peptide T on CMRglc with its effect on the progression of the disease is being tested. To determine whether differences in cerebral metabolism observed between drug abusers and matched controls represent a predisposition toward drug abuse or changes due to drug abuse, rates of cerebral metabolism and blood flow in twins discordant for drug abuse are being studied. Magnetic resonance imaging (MRI) is used to study brain structure, as related to neuropsychological performance in substance abusers. Correlations between planimetric MRI measurements and neuropsychological tests indicate that deficits in frontal areas of the brain may mediate the neuropsychological performance impairments in substance abusers. New studies will concentrate on relations of volumetric MRI measurements to performance and personality measures in substance abusers.

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Morgan MJ, NJ Cascella, JM Stapleton, RL Phillips, BCK Yung, DF Wong, EK Shaya, and ED London: Sensitivity to subjective effects of cocaine in drug abusers: Relation to cerebral ventricular size. Am. J. Psychiatry., in press.

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Newlin DB, MB Pretorius, CJ Wong, JM Stapleton, and ED London: Acute intravenous cocaine reduces cardiac vagal tone in cocaine abusers. NIDA Res. Monogr., in press.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00202-10 NDAS

PERIOD COVERED

October 1 1992 to September 30 1993

TITLE OF PROJECT

Physiological Effects of Opioids

PRINCIPAL INVESTIGATOR

P.I.	ED London	Chief	Neuroscience Branch
	JA Bell	Pharmacologist	Neuroscience Branch
	AS Kimes	Biologist	Neuroscience Branch
	DB Vaupel	Pharmacologist	Neuroscience Branch
	SJ Grant	Senior Staff Fellow	Neuroscience Branch

COOPERATING UNITS

LAB/BRANCH

Neuroscience Branch

SECTION

Neuroimaging and Drug Action

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER.
3.26	2.73	0.53

CHECK APPROPRIATE BOXES

☒ (A) Human ☐ (b) Human Tissue ☐ (c) Neither

☐ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK

In vitro, animal and human studies are performed to elucidate mechanisms of opioid action and to develop new therapeutic modalities. Chronic morphine treatment produces dependence and tolerance in neonatal rats, as seen in electrophysiological assays of synaptic activity in the isolated spinal cord. Chemically and electrically evoked responses of nociceptive neurons show opioid tolerance that is not prevented by co-treatment with MK-801. Spontaneous and precipitated opioid withdrawal (OW) can be demonstrated also. Recordings from brain slices show that inhibition of nitric oxide synthase (NOS) diminishes the development of tolerance to morphine in noradrenergic neurons of the locus coeruleus (LC) of adult morphine-treated rats, suggesting a cellular substrate for the involvement of nitric oxide in OW. Behavioral experiments demonstrate that inhibiting NOS reduces some signs of OW. Potencies of compounds tested in this system parallel their relative potencies in inhibiting NOS, consistent with the view that NOS inhibition is the relevant mechanism for inhibiting OW. Other work in rats shows that behavioral signs of OW and cerebral hypermetabolism occur when methylnaloxonium, an opioid antagonist, is injected directly into the LC of morphine-dependent rats. In drug-naive rats, buprenorphine mimics the effect of morphine on cell firing, but in morphine-dependent rats buprenorphine mimics naloxone, consistent with the hypothesis that the actions of buprenorphine, a partial opioid agonist, vary with the state of opioid dependence. An assessment in human volunteers of the interactions of the Ca+2 channel antagonist verapamil with morphine shows that verapamil antagonizes the positive affective changes produced by morphine and potentiates the analgesic effects of morphine.

US Patent # 5,225,440 "Attenuation of the opioid withdrawal syndrome be inhibitors of nitric oxide synthase" ED London and AS Kimes inventors, granted July 6, 1993

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Vaupel DB, WR Lange, and ED London (1993): Effects of verapamil on morphine-induced euphoria, analgesia and respiratory depression in humans. J. Pharmacol. Exp. Ther., in press.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00206-08 NDAS

PERIOD COVERED

October 1 1992 to September 30 1993

TITLE OF PROJECT

Biological and Biochemical Characterization of Sigma Receptors

PRINCIPAL INVESTIGATOR

P.I.	TP Su	Research Chemist	Neuroscience Branch
	DJ McCann	Senior Staff Fellow	Neuroscience Branch
	S Yu	Visitin gFellow	Neuroscience Branch
	LI Tsao	Staff Fellow	Neuroscience Branch

COOPERATING UNITS

LAB/BRANCH

Neuroscience Branch

SECTION

Neuroimaging and Drug Action

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
2.9	2.9	0

CHECK APPROPRIATE BOXES

☐ (A) Human ☐ (b) Human Tissue ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

@This project delineates biochemical, chemical, and pharmacological properties of sigma receptors and ligands. At high concentrations, (Tris)hydroxymethyl(aminomethane) HCl (Tris) inhibits binding to sigma receptors in a dose-dependent and competitive manner. This observation suggests that certain pharmacological responses mediated by sigma receptors could be masked by Tris. Brain homogenate binding assays reveal that sigma-1 and sigma-2 receptor subtypes exhibit different ontogenetic patterns. Sigma-1 receptors remain relatively unchanged from prenatal to postnatal ages (-3 to 90 days). Sigma-2 receptor densities are 10-fold higher at 3 days before birth than at day 30 at which time the densities of sigma-2 and sigma-1 receptors are similar. Subcellular distributions of sigma-1 and sigma-2 receptors do not differ. No differences in sigma-1 or sigma-2 receptors are found when comparing genetically dystonic rats with their normal littermates. Solubilized sigma receptors from rat liver can be resolved into two components by charge partition chromatography. Saturation analysis reveals similar affinities for radiolabeled d-N-allylnormetazocine to both components, suggesting that they do not represent sigma-1 and sigma-2 receptors. Further purification of the receptors is underway.

Su T-P (1993): Delineating biochemical and functional properties of sigma receptors: Emerging concepts. CRC Critical Reviews in Neurobiology., in press.

Su T-P and J-L Junien (1993): Sigma receptors in the central nervous system and periphery. In: The Sigma Receptors, Y. Itzhak, ed., Academic Press, London, in press.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00215-01 VUL

PERIOD COVERED

October 1 1992 to September 30 1993

TITLE OF PROJECT

The Role of Race/Ethnicity in Crack Cocaine Use

PRINCIPAL INVESTIGATOR

P.I.	H Chilcoat	Staff Fellow	Etiology Branch
	C Schutz	Visiting Fellow	Etiology Branch
	J Anthony	Senior Staff Fellow	Etiology Branch
	F Wagner	Guest Worker	Etiology Branch

COOPERATING UNITS

LAB/BRANCH

Etiology Branch

SECTION

Vulnerability

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
0.8	0.8	0

CHECK APPROPRIATE BOXES

☐ (A) Human ☐ (b) Human Tissue ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

Reports on the prevalence and incidence drug use commonly list separate estimates for various drugs by race/ethnicity. However, this can be somewhat misleading because reporting results in this way can infer that race or ethnicity by themselves are important factors in drug use. Several researchers recently have advocated that race/ethnicity be used as markers for other factors that might be related to race, such as socio-economic indicators, neighborhood characteristics, cultural variables, and impact of racism or discrimination. For this reason, this project has investigated the meaning of racial/ethnic differences in crack use using data from the National Household Survey on Drug Abuse (NHSDA).

Crack is one of the only drugs for which there are differences by race/ethnicity. In the 1990 NHSDA, the lifetime prevalence of crack use for African Americans was 3.1% compared to 1.6 % for Hispanics and 1.1% for Whites. However, in an analysis that held neighborhood constant, there was no overall difference between African- and White-Americans; the odds of crack use for Hispanics was only half that for Whites. An investigation of age by race interactions indicated that, even when neighborhood was held constant, the odds of lifetime crack use for African-Americans 30 - 35 years old was 2.5 that of White-Americans in the same age group. Further, the African-American crack users were more likely to have used in the last year. An examination of the trends in crack use indicated that lifetime prevalence of crack use for African-Americans increased from 5% in 1988 to 8% in 1990, whereas there was little change for other age groups or race/ethnicities.

A parallel analysis was conducted that examined only Hispanics, using data from the 1988, 1990, and 1991 NHSDA and employing a post-stratification strategy that held neighborhood constant. The respondent's choice of the Spanish version of the survey instrument was used as an indicator of degree of acculturation. This analysis indicated that the odds of crack use for Hispanics who used the Spanish version of the survey instrument was approximately one-third that of those using the English version. An analysis of the interaction between language version and Hispanic origin indicated that this finding was most pronounced among Mexican-Americans, where the odds of crack use for those taking the Spanish version was one-sixth that for the English version. These findings point to the importance of degree of acculturation in initiating crack use.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00216-01 VUL

PERIOD COVERED

October 1 1992 to September 30 1993

TITLE OF PROJECT

Risk Factors and Vulnerability Markers of Injecting Drug Use

PRINCIPAL INVESTIGATOR

P.I.	C Schutz	Visiting Fellow	Etiology Branch
	H Chilcoat	Staff Fellow	Etiology Branch
	J Anthony	Senior Staff Fellow	Etiology Branch

COOPERATING UNITS

LAB/BRANCH

Etiology Branch

SECTION

Vulnerability

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
0.5	0.5	0

CHECK APPROPRIATE BOXES

☐ (A) Human ☐ (b) Human Tissue ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

Injecting drug use is a major public health concern. Use of needles to inject drugs for non-medical reasons generally signifies a later stage of drug use as well as increased involvement in multiple drug use. It is associated with a number of health hazards. These health hazards not only include the drug-induced hazards such as drug dependence and overdose, but additionally the method-induced health hazards such as infections including hepatitis, endocarditis and HIV/AIDS. There has been an almost complete lack of research regarding the etiology of injecting drug use, and thus our knowledge of causes and risk factors of injecting drug use are limited.

A few sporadic clinical studies have indicated that inhalant use might prove to be a modifiable risk factor or alternately an important vulnerability marker for injecting drug use. We used data compiled in the 1990 National Household Survey on Drug Abuse to test this association in an epidemiologic study, statistically adjusting for plausible confounders, including marijuana use. Based on multiple logistic regression models, respondents using both marijuana and inhalant were 88.1 times more likely to have injected drugs (95% confidence interval=123.7-62.7) than those who had neither used inhalants nor marijuana. Those using inhalants, but not marijuana were an estimated 45.3 times more likely to have injected drugs (95% CI=75.8-28.1). The odds ratio was 18.6 for those who had used marijuana, but not inhalants (95% CI= 25.-13.3). This study is a first step in understanding the etiologic conditions giving rise to injecting drug use.

Schütz CG, Chilcoat HD, Anthony JC. (in press) The association between sniffing inhalants and injecting drugs. Comprehensive Psychiatry.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00220-01 MNS

PERIOD COVERED

October 1 1992 to September 30 1993

TITLE OF PROJECT

Opiate Receptors: Cloning and Expression

PRINCIPAL INVESTIGATOR

P.I.	JB Wang	Guest Worker	Molecular Neurobiology Branch
	Y Imai	Visiting Fellow	Molecular Neurobiology Branch
	G Uhl	Branch Chief	Molecular Neurobiology Branch
	P Gregor	Staff Fellow	Molecular Neurobiology Branch
	C Spivak	Pharmacologist	Molecular Neurobiology Branch

COOPERATING UNITS

CM Eppler, American Cyanimid Co.

LAB/BRANCH

Molecular Neurobiology Branch

SECTION

Molecular Neurobiology

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
1.8	1.8	

CHECK APPROPRIATE BOXES

☐ (A) Human ☐ (b) Human Tissue ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

Opiate receptors recognize endogenous opioid peptide neurotransmitters and exogenous opiate drugs of high abuse liability and analgesic benefits. Mu opiate receptors that recognize morphine with very high affinity are of particular interest. In order to improve understanding of these key elements in mediating opiate addictions, these workers have worked to clone opiate receptor cDNAs and thus elucidate structural and functional receptor features over this FY.

Rat brain cDNAs whose predicted translation products display moderate identity with sequences of the recently-described delta-opiate receptor were identified through polymerase chain reaction and cDNA homology approaches. One cDNA recognizes a 10.5 kb mRNA that is expressed in thalamic neurons. COS cell expression confers naloxonazine-, NA+- and GTP-sensitive binding of mu, but not delta or k opioid ligands. Expressing cells bind morphine and other opioid peptide ligands with nanomolar or subnanomolar affinities, defining a mu opiate receptor that avidly recognizes analgesic and euphoric opiate drugs and opioid peptides.

Wang J-B, Imai Y, Eppler CM, Gregor P, Spivak C, Uhl GR. mu Opiate receptor/binding protein: cDNA cloning and expression, PNAS.USA 1993;in press.

Eppler CM, Hulmes JD, Wang J-B, Johnson B, Corbett M, Luthin DR, Uhl GR, Linden J. Purification and partial amino acid sequence of a mu opioid receptor from rat brain, J Biol Chem 1993;in press.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00221-01 MNS

PERIOD COVERED

October 1 1992 to September 30 1993

TITLE OF PROJECT

Human and Murine Dopamine Transporter Gene Analyses and Dopaminergic Disorders

PRINCIPAL INVESTIGATOR

P.I.	D Vandenbergh	Senior Staff Fellow	Molecular Neurobiology Branch
	D Donovan	Senior Staff Fellow	Molecular Neurobiology Branch
	M Perry	Guest Worker	Molecular Neurobiology Branch
	GS Bird	Guest Worker	Molecular Neurobiology Branch

COOPERATING UNITS

O Hurko, Johns Hopkins School of Medicine
E Gershon, Clinical Neurogenetics Branch, NIMH
J Gelertner, Yale University

LAB/BRANCH

Molecular Neurobiology Branch

SECTION

Molecular Neurobiology

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
2.1	1.35	0.75

CHECK APPROPRIATE BOXES

☒ (A) Human ☐ (b) Human Tissue ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

The dopamine transporter/cocaine receptor (DAT) is the site at which cocaine exerts rewarding/reinforcing effects as well as playing a central role in termination of dopamine neurotransmission. Cloning of rat and human DAT cDNAs by Addiction Research Center scientists during the preceding FY provided primary sequence information and cDNA clones that facilitated isolation of genomic clones from rodent and human, development of polymorphic genetic markers, and application of these markers to human disorders hypothesized to involve dopaminergic system dysfunction or those treatable with dopaminergic agents.

Screening of phage and cosmid genomic libraries from human and murine embryonic stem cells resulted in identification of several human and murine genomic clones of more than 20 kb (murine) and more than 9 kb (human), respectively. Attempts to drive expression of reporter genes with several constructs including the murine "promoter/enhancer" sequences were unrevealing, suggesting the possibility of strong cell-type specificity in the transporter's expression.

Polymorphic genetic human transporter gene markers were used for analysis individuals with Tourette's syndrome and Parkinson's disease. No linkage between the DAT gene and Tourette's Syndrome was demonstrated in two large and 10 small kindreds; 5 centimorgans on either side of the DAT gene can be excluded by these analyses. No variation in the number of copies of the VNTR passed between generations has been detected in these families. No association between Parkinson's disease and DAT gene markers can be identified.

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Uhl GR, Kitayama S. A cloned dopamine transporter: potential insights into parkinson's disease pathogenesis. In: Narabayashi H, Nagatsu T, Yanagisawa N, Mizuno Y, eds. Parkinson's disease: from basic research to treatment, advances in neurology. New York: Raven Press, Ltd., 1993;321-4.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00222-01 MNS

PERIOD COVERED

October 1 1992 to September 30 1993

TITLE OF PROJECT

Human Synaptic Vesicular Monoamine Transporter: Cloning and Expression

PRINCIPAL INVESTIGATOR

P.I.	C Surratt	Senior Staff Fellow	Molecular Neurobiology Branch
	A Persico	Visiting Fellow	Molecular Neurobiology Branch
	G Uhl	Branch Chief	Molecular Neurobiology Branch

COOPERATING UNITS

A Gonzales, Dept of Neuroscience, Johns Hopkins

LAB/BRANCH

Molecular Neurobiology Branch

SECTION

Molecular Neurobiology

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
0.86	0.86	0

CHECK APPROPRIATE BOXES

☐ (A) Human ☐ (b) Human Tissue ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

The synaptic vesicle monoamine transporter (SVMT) transports monoamine neurotransmitters into synaptic vesicles, and recognizes amphetamines including MDMA ("ecstasy") as substrates. Amphetamine is a weak bases that may enter the vesicle via this transporter and/or by passive diffusion to elevate the pH of the vesicle's acidic interior and precipitate release of stored neurotransmitter.

In the current FY, a human cDNA clone which encodes the SVMT protein has been isolated and sequenced. The human protein of 514 amino acids shares 92% amino acid identity with a previously isolated rat homolog, but displays slight differences in consensus sites for glycosylation and phosphorylation. The human SVMT gene mapps to chromosome 10q25 using Southern blotting and fluorescent in situ hybridization approaches. Northern analysis reveals expression of 3 kb mRNA in human brainstem and 4.8 kb mRNA in hypothalamus. Substantial expression in human nigra compacta neurons and in apparent histaminergic hypothalamic neurons in rat was detected. COS cell hSVMT expression yielded nanomolar affinities for tetrabenazine and reserpine, micromolar affinities for haloperidol, GBR-12909, serotonin, mazindol, nomifensin and d-amphetamine, and millimolar affinities for dopamine, epinephrine, norepinephrine and histamine.

Surratt CK, Persico AM, Yang X-D, Edgar SR, Bird GS, Hawkins AL, Griffin CA, Li X, Jabs EW, Uhl GR. A human synaptic vesicle monoamine transporter cDNA predicts post-translational modifications, reveals chromosome 10 gene localization and identifies TaqI RFLPS, FEBS Lett 1993;318(3):325-30.

Gonzalez AM, Walther D, Pazos A, Uhl GR. Synaptic vesicular monoamine transporter expression: distribution and pharmacologic profile, Mol Brain Res 1993;in press.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00223-01 MNS

PERIOD COVERED

October 1 1992 to September 30 1993

TITLE OF PROJECT

GABA Receptors: Rho 1, Alpha/Beta and Neurosteroid Effects

PRINCIPAL INVESTIGATOR

P.I.	T Kusama	Visiting Associate	Molecular Neurobiology Branch
	CE Spivak	Pharmacologist	Molecular Neurobiology Branch
	JB Wang	Guest Worker	Molecular Neurobiology Branch
	V Dawson	IRTA	Molecular Neurobiology Branch
	GR Uhl	Branch Chief	Molecular Neurobiology Branch

COOPERATING UNITS

LAB/BRANCH

Molecular Neurobiology Branch

SECTION

Molecular Neurobiology

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER
1.5	1.5	0

CHECK APPROPRIATE BOXES

☐ (A) Human ☐ (b) Human Tissue ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

The recently-identified GABA Rho1 receptor allows the examination of GABA receptor structure/function, since it expresses well as a homooligomer. This receptor is insensitive to bicuculline, baclofen and modulators of GABA A receptor, and desensitizes very slowly facilitating characterization of this receptor's binding site for agonists and competitive antagonists. The agonist profile of the GABA Rho1 receptor was strikingly different from that of the typical GABA A receptor in the Xenopus oocyte expression system. Studies of cyclic agonists, such as THIP and isonipecotic acid, active at GABA A receptors but virtually inert at GABA Rho1 receptors, indicate that the recognition of site of the GABA Rho1 receptor selects for a more extended conformation of agonists.

The GABA Rho2 receptor, while closely resembling GABA Rho1 in primary sequence, showed 20% difference in the N-terminal region. Like Rho1, it functioned as a homooligomer, but the currents responded to GABA more slowly and their maxima were conspicuously smaller. Concentration response curves yielded similar agonist profiles for Rho1 and Rho2, though Rho2 generally had lower Kd values by a factor of about two-fold. Among the 9 agonists tested, the outstanding exception was imidazole-4-acetic acid. Its Kd was 16-times smaller, its maximum current (with respect to the maximum produced by GABA) 7-times greater, and its Hill coefficient double at Rho2 in comparison to Rho1.

Sixteen mutations in the Rho1 sequence were constructed. Mutations in residue 141H diminished the affinity of GABA or abolished the responses, whereas most other mutations increased affinity. Most mutations, however, seemed to diminish the maximum current. The mutations had variable effects on the Hill coefficient, nH = 2.26 in Rho 1. Some decreased nH to as little as 1.24, but mutations at residue 316, in the extracellular domain between membrane spanning regions 2 and 3, increased it to as high as 3.9 The maximum responses to THIP remained low in all mutations, indicating that the receptors retained Rho1 -like selectivity for agonists. These studies suggest regions in the receptor's structure that may be crucial in agonist recognition or transduction, and that may facilitate cooperative interaction among subunits.

Kusama T, Spivak CE, Whiting P, Dawson VL, Schaeffer JC, Uhl GR. Pharmacology of GABA Rho1 and GABA alpha/beta receptors expressed in Xenopus oocytes and COS cells, Br J Pharmacol 1993;109:200-6.

Kusama, T., Wang, T.-L., Guggino, W.B., Cutting, G.R., and Uhl, G.R.: GABA Rho2 receptor pharmacological profile: GABA recognition site similarities to Rho1, Eur. J. Pharmacol 1993;245:83-4.

Shimada S, Cutting G, Uhl GR. -Aminobutyric acid A or C receptor? -Aminobutyric acid 1 receptor RNA induces bicuculline-, barbiturate-, and benzodiazepine-insensitive -aminobutyric acid responses in Xenopus oocytes, Mol Pharm 1992;41:683-7.

Spivak, C.E.: Desensitization and noncompetitive blockade of a GABA A receptor from ventral midbrain neurons by the neurostroid dehydroepiandrosterone sulfate, Synapse 1993;in press.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00224-01 MNS

PERIOD COVERED

October 1 1992 to September 30 1993

TITLE OF PROJECT

Glutamate Receptors: Molecular Diversity, Functional Properties and Genetics

PRINCIPAL INVESTIGATOR

P.I.	P Gregor	Staff Fellow	Molecular Neurobiology Branch
	GR Uhl	Branch Chief	Molecular Neurobiology Branch
	X Yang	Guest Worker	Molecular Neurobiology Branch

COOPERATING UNITS

LAB/BRANCH

Molecular Neurobiology Branch

SECTION

Molecular Neurobiology

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER
1.31	0.91	0.4

CHECK APPROPRIATE BOXES

☐ (A) Human ☐ (b) Human Tissue ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

Glutamate is the principal excitatory neurotransmitter at most synapses, and strongly modulates dopaminergic pathways involved in addictive behaviors. There are two different types of glutamate gated-ion channels, NMDA receptors and non-NMDA receptors. The NMDA receptors (produced by genes NR1, NR2A-NR2D) have attracted considerable attention due to its role in long-term potentiation (LTP), a proposed form of memory. NMDA receptors are also sites of action of the hallucinogenic street drug phencyclidine (PCP; "angel dust"). Non-NMDA receptors are encoded by genes GluR1-GluR7, KA-1 and KA-2, and represent the principal sites of glutamatergic transmission.

In the course of molecular characterization of glutamate receptors, we have cloned four new glutamate receptor subunit variants. Subunits NR1b and NR1c define new splice variants of the NR1 subtype of glutamate receptors. Sequencing revealed that NR1b differs from NR1a by the presence of a 21 amino acid insert near its amino-terminus and by a different sequence of the carboxy-terminus. Properties of NR1b were studied in the oocyte expression system. NR1b channels exhibited a lower affinity for NMDA and glutamate, whereas affinities for PCP and glycine were nearly identical. Spermine potentiation of NR1b receptors was abolished, probably due to the amino-terminal insertion which has a net positive charge. Furthermore, NR1b channels were potentiated by protein kinase C about 20-fold, what is much less than the potentiation of NR1a channels, about 4-fold. These observations show that alternative splicing plays a role in generating NMDA receptor channels with different properties. Phosphorylation of NMDA receptors by protein kinase C regulates its channel activity and may have a role in LTP. Elucidation of the functional significance of alternately spliced NMDA receptors may have significance for interaction with drugs such as PCP. In addition, we identified two glutamate receptor subunit cDNAs termed GluR5-1d and GluR6-2 which define new isoforms of kainate receptors with altered structure of the carboxy-terminal domain. These novel subunits are apparently generated by alternative splicing of a facultative intron. The position of this intron has been predicted from the gene structure of the kainate binding protein (KBP), another glutamate receptor gene which we have characterized in detail. Genetic mapping of several glutamate receptor genes revealed that the GLUR5 gene is located on human chromosome 21 close to the familial amyotrophic lateral sclerosis locus and in the region implicated in Down's Syndrome. Physical mapping of the GLUR5 gene with yeast artificial chromosomes showed that the GLUR5 gene is located between APP and SOD1 genes at 21q22.1 The relatively large size of the GLUR5 gene, 400-500 kb, raises questions about its functional significance.

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egor P, Yang X, Mano I, Takemura M, Teichberg VI, Uhl GR. Organization and expression of the gene coding chick kainate binding protein, a member of the glutamate receptor family, Mol Brain Res 1992;16:179-.

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egor P, O'Hara BF, Yang X, Uhl GR. Expression and novel subunit isoforms of glutamate receptor genes uR5 and GluR6, NeuroReport 1993;in press.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00225-01 GS

PERIOD COVERED

October 1 1992 to September 30 1993

TITLE OF PROJECT

Genetic Approaches to Characterizing Drug Responses and Vulnerabilities

PRINCIPAL INVESTIGATOR

P.I.	RJ Marley	Senior Staff Fellow	Molecular Neurobiology Branch
	LL Miner	Senior Staff Fellow	Molecular Neurobiology Branch
	N Goodman	Pharmacologist	Molecular Neurobiology Branch
	K Shimosato	Visiting Fellow	Molecular Neurobiology Branch
	GR Uhl	Branch Chief	Molecular Neurobiology Branch

COOPERATING UNITS

LAB/BRANCH

Molecular Neurobiology Branch

SECTION

Genetics

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
3.49	2.49	1

CHECK APPROPRIATE BOXES

☐ (A) Human ☐ (b) Human Tissue ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

There are large individual differences among humans and animals in behavioral, physiological and toxicological responses to drugs of abuse. These individual differences in behavioral responses to drugs also display substantial genetic and environmental influences, are continuously distributed, and appear to be influenced by many genes rather than one or two major genes. For these reasons, application of several of the techniques of genetics and molecular biology could be helpful in identification of genetic influences in readily-studied experimental animals that could shed light on human interindividual differences, and identify genes potentially responsible for behavioral variation in drug responses in these animals.

Differences between several inbred mouse strains' normal responses to psychomotor stimulants and "kindling" induced by repetitive drug administration have been sought and correlated with strain-to-strain differences in biochemical parameters related to opiate receptor, GABAA receptor, and dopamine transporter densities and/or function. Recombinant inbred strains have been tested for cocaine-induced locomotor responses and sensitization. Animals from a heterogenous stock have been tested for cocaine-induced locomotor activation, and have been used to establish a genetic selection paradigm to ask if selection for cocaine-induced locomotion also selects for other cocaine-induced functions, including psychomotor stimulant conditioned place preference measures. Each of these approaches will allow improved assessment of genetic influences in substance abuse, and analyses of the recombinant inbred strain comparisons will allow chromosomal mapping of specific genes contributing to the strain differences through quantitative trait locus approaches.

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arley RJ, Elmer GI, Goldberg SR. The use of pharmacogenetic techniques in drug abuse research, harmacol Ther 1992;53:217-37.

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arley RJ, Collins AC, Elmer GI, Sudakov SK, Belknap J, McClearn GE, Pickens RW, Goldberg SR. Genetic pproaches to understanding the actions of drugs of abuse. In: Problems of drug dependence 1992: roceedings of the 54th Annual Scientific Meeting of the College on Problems of Drug Dependence 1992;NIDA es Mongr 1993;132:47-51.

annerud CA, Marley RJ, Alastra AJG, Cohen C, Goldberg SR. Contingent tolerance to chlordiazepoxide: ehavioral, pharmacological and biochemical selectivity, J Pharmacol Exp Ther 1993;in press.

arley RJ, Shimosato K, Elmer GI, Miner LL. Pharmacogenetic approaches to drug dependence. In: onnacott S, Lunt GG, eds. Biochemistry of Drug Dependence. London: Portland Press, 1993;in press.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00226-02 MPS

PERIOD COVERED

October 1 1992 to September 30 1993

TITLE OF PROJECT

The Cocaine Receptor: Biochemical and Molecular Studies

PRINCIPAL INVESTIGATOR

P.I.	MJ Kuhar	Chief	Neuroscience Branch
	A Patel	Senior Staff Fellow	Neuroscience Branch
	R Vaughan	Staff Fellow	Neuroscience Branch
	S Pogun	Visiting Scientist	Neuroscience Branch
	C Cerruti	Visiting Fellow	Neuroscience Branch

COOPERATING UNITS

LAB/BRANCH

Neuroscience Branch

SECTION

Molecular Pharmacology

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
4	3	1

CHECK APPROPRIATE BOXES

☐ (A) Human ☐ (b) Human Tissue ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

The goal of this project is to elucidate the biochemical properties of the cocaine receptor or the dopamine transporter. We have previously shown that the dopamine transporter in the rat striatum and nucleus accumbens are heterogeneous in molecular weight. When the transporters were treated with N-glycanase, the molecular weight of both transporters were reduced significantly and the apparent differences were either absent or minimized. This suggests that the factor in heterogeneity is differences in glycosylation although it is not possible to rule out other sources of heterogeneity as well. We have also prepared anti-peptide antibodies to the dopamine transporter and some of these transporter antibodies are useful for immunoprecipitation and western blotting.

There are species differences in the cloned cDNAs for dopamine transporters. Accordingly, we examined the molecular weight of transporters, post-mortem changes as well as glycosylation differences among the different species. The molecular weights differed as one would expect based on differences predicted by the cDNA sequences. Dopamine transporters bind cocaine and its analogues with two sites of differing affinities. This has raised the issue of whether or not there are more than one type of dopamine transporter or whether heterogeneity due possibly to glycosylation could account for the different sites. Accordingly, a cDNA for the dopamine transporter was transfected into COS cells and, these cells expressed two binding sites for cocaine. These data indicate that the heterogeneous binding occurs from a single protein which must be modified in different ways.

We have examined the distribution of dopamine transporter mRNA in brain by in situ hybridization analysis. We find that cell groups found in the midbrain contain high levels of mRNA while cell groups outside of the midbrain contain very low levels of mRNA for the transporter.

We have made substantial progress in understanding the nature of the dopamine transporter protein, how it is processed and where it is produced.

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Few R, Patel A, Vaughan RA, Wilson A, Kuhar MJ. Microheterogeneity of Dopamine Transporters in Rat Striatum and Nucleus Accumbens, Brain Research 1991; 584:266-271.

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Patel A, Uhl GR and Kuhar MJ. Species Differences in Dopamine Transporters: Postmortem Changes and Glycosylation Differences. J. Neurochem. 61: 496-500, 1993.

Ferruti C, Walther DM, Kuhar MJ and Uhl GR. Dopamine Transporter mRNA Expression is Intense in Rat Midbrain
Neurons and Modest Outside Midbrain. Mol. Brain Research 18:181-186, 1993.

Crouard A, Pelaprat D, Boja JW, Carroll FI, Vial M, Kuhar MJ, Rostene W. Potent cocaine Analogs, Inhibit [3H]Dopamine Uptake in Rat Mesencephalic Cells in Primary Cultures: Pharmacological Selectivity of Embryonic Cocaine Sites. Brain Research, in press, 1993

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00227-01 CPS

PERIOD COVERED

October 1 1992 to September 30 1993

TITLE OF PROJECT

Clinical Neurological Examination in Cocaine Abusers

PRINCIPAL INVESTIGATOR

P.I.	JL Cadet	Senior Staff Fellow	Clinical Pharmacology Branch
	WR Lange	Clinical Director	Medical Affairs
	RB Rothman	Chief	Clinical Pharmacology Branch
	JE Henningfield	Chief	Clinical Pharmacology Branch

COOPERATING UNITS

LAB/BRANCH

Clinical Pharmacology Branch

SECTION

Clinical Psychopharmacology

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER
2	1	1

CHECK APPROPRIATE BOXES

☒ (A) Human ☐ (b) Human Tissue ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

The purpose of this project is to assess the neurological status of individuals who have abused cocaine over a long period of their lives. The acute and chronic use of cocaine is associated with medical and neuropsychiatric abnormalities. The neuropsychiatric disorders include seizure, psychosis, subarachnoid hemorrhage, and thromboembolic phenomena. Most of these abnormalities occur in the acute setting of cocaine use. However, we are aware of no studies which used the detailed classical neurological examination in order to classify possible effects of the drugs on the central (CNS) and peripheral (PNS) nervous system. As a first step towards the elucidation of cocaine effects on the nervous system, we have thus started to carry out thorough neurological examination in subjects who are chronic cocaine abusers and who are seronegative for HIV. Subjects with a long history of cocaine abuse receive a complete medical and neurological examination. The results of these examinations have shown some consistent findings. A total of twenty subjects were evaluated. Four subjects were dropped because of positive autoantibodies. The abnormal findings on the neurological examination included horizontal nystagmus, abnormal eye pursuit, abnormal saccades, decreased reflexes, and increased jaw jerk. Vibration and position senses were also abnormal. The presence of nystagmus and increased jaw jerk in these subjects may be related to cocaine effects on brainstem pathways. The reflex and sensory abnormalities appear to correspond to a bilateral symmetric neuropathy. When taken together, these results suggest that cocaine may cause deleterious effects on the nervous system by causing constriction of the vasa nervorum which supply the PNS. In addition to providing preliminary documentation of the damage done to the PNS by cocaine, these findings suggest a new line of investigation which will focus on the clinical neurological consequences of cocaine abuse.

adet, J.L., Gendron, T., Lange, W.R., Henningfield, J.E., and Rothman, R.B. The Clinical Neurological xamination in Chronic Cocaine Abusers: Preliminary Findings. NIDA Monograph Series (in press).

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00228-01 CPS

PERIOD COVERED

October 1 1992 to September 30 1993

TITLE OF PROJECT

Drug Induced Toxicity and Free Radicals

PRINCIPAL INVESTIGATOR

P.I.	JL Cadet	Senior Staff Fellow	Clinical Pharmacology Branch
	RB Rothman	Chief	Clinical Pharmacology Branch
	P Sheng	Visiting Fellow	Clinical Pharmacology Branch

COOPERATING UNITS

LAB/BRANCH

Clinical Pharmacology Branch

SECTION

Clinical Psychopharmacology

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
1	1	0

CHECK APPROPRIATE BOXES

☐ (A) Human ☐ (b) Human Tissue ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

This project assesses the role that free radicals might play in the neurotoxic effects associated with amphetamine analogs. Towards that end, we determined the effects of drug of abuse on the dopamine and serotonin systems in adult transgenic mice which overexpress the scavenging enzyme, superoxide dismutase. Oxygen-based radicals are toxic compounds that have been implicated in the causation of a number of neurotoxic and neuropathological events. More recently, because intact dopamine systems are necessary for the manifestation of methamphetamine-induced neurotoxicity, it was suggested that the deleterious effects of these drugs of abuse, including the by-products of their synthesis, might be related to the production of oxygen-based and of other reactive compounds. Several enzymes work in concert to protect the organisms against the ravages of active oxygen species. These include catalase, glutathione peroxidase, and superoxide dismutase.

The neurotoxic effects of MPTP were evaluated in a transgenic mouse model which over express the human SOD enzyme. These studies revealed that these animals are protected against the toxic effects of MPTP on the nigrostriatal dopamine system. Administration of methamphetamine (METH) also causes significant depletion in a number of mammalian species. The effects of METH were also tested in the SOD-Tg mice. In Non-Tg mice, acute METH administration caused significant decreases in DA and dihydroxyphenyl acetic acid (DOPAC) in the striata and cortices. In contrast, there were no significant changes in striatal or cortical DA in the SOD-Tg mice. The effects of METH on DOPAC were also attenuated in both structures of these SOD-Tg mice. Chronic administration of METH caused depletion of DA and DOPAC in only the striata of Non-Tg mice. These results suggest that METH-induced neurotoxicity in mice might be secondary to the increased production of superoxide radicals generated during the metabolism of dopamine via monoamine oxidase.

Cadet, J.L., Kujirai K., Carlson, E., Epstein, C.J. Autoradiographic Distribution of [3H]Neurotensin Receptors in the Brains of Superoxide Dismutase Transgenic Mice. Synapse 14:24-33 (1993).

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00229-01 CPS

PERIOD COVERED

October 1 1992 to September 30 1993

TITLE OF PROJECT

Effects of Subdivisional 6-OHDSA Injections on Cocaine Induced Behaviors

PRINCIPAL INVESTIGATOR

P.I.	JL Cadet	Senior Staff Fellow	Clinical Pharmacology Branch
	RB Rothman	Chief	Clinical Pharmacology Branch
	JS Partilla	Lab Manager	Clinical Pharmacology Branch
	P Sheng	Visiting Fellow	Clinical Pharmacology Branch

COOPERATING UNITS

LAB/BRANCH

Clinical Pharmacology Branch

SECTION

Clinical Psychopharmacology

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
3	2	1

CHECK APPROPRIATE BOXES

☐ (A) Human ☐ (b) Human Tissue ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

These studies assess the distribution of [125I]RTI-55-labeled dopamine and serotonin uptake sites in the rat brain. Cocaine exerts its addictive properties through the blockade of DA uptake sites. Studies have been done to characterize the specific effects of cocaine on the brain, using ligands which bind at more than the DA uptake sites. Effort is being made to develop a ligand which is sensitive and specific for DA uptake sites. One of these ligands is [125I]RTI-55. We determined the distribution of these sites in the rat central nervous system in the present study. In addition, we evaluated the effects of 6-OHDA lesions in the nigrostriatal DA pathway. Unilateral lesions of the nigrostriatal dopaminergic pathway were performed by the stereotaxic application of 6-OHDA in the caudate-putamen. Sections were taken at the levels of the NAc, CPu, and the substantia nigra pars compacta (SNpc). Autoradiographic distribution of total [125I]RTI-55 binding (no blocking agents) shows high binding densities in the NAc, the olfactory tubercle, the CPu, and in the SNpc. Total binding shows a laminar distribution in the cortex. 6-OHDA caused marked decreases in [125I]RTI binding sites in the NAc and the CPu. Sections incubated in the presence of paroxetine which blocks binding to 5-HT uptake sites caused a total disappearance of binding in the cortex. There were marked decreases in paroxetine-insensitive [125I]RTI binding sites in the CPu and in the SNpc on the side of 6-OHDA lesions. Sections labeled with [125I]RTI in the presence of LR1111 which blocks binding of the ligand to dopamine uptake sites shows marked decreases in [125I]RTI55 binding in the CPu. The laminar pattern of the distribution [125I]RTI in the cortex was still apparent even in the presence of LR111. There were small differences between the two sides of the brains of animals that had gotten 6-OHDA lesions. These results suggest that [125I]RTI55 binds to both striatal DA and 5-HT uptake sites. In the presence of paroxetine as a blocker, [125I]RTI may be a good ligand to label the DA uptake site in the striatum.

Cadet, J.L., and Zhu, S.M. The Intrastriatal 6-Hydroxydopamine Model of Semiparkinsonism: Quantitative Receptor Autoradiographic Evidence of Correlation Between Circling Behavior and Presynaptic as well as Postsynaptic Nigrostriatal Dopaminergic Markers in the Rat. Brain Research 595:316-326 (1992).

Cadet, J.L., Ordinez, S., C.M. Dersch, Brockington, A., Becketts, K.M., Partilla, J.S., de Costa, B.R., Rice, K.C., Carroll, F.I., Akunne, H.C., and Rothman, R.B. Quantitative Autoradiographic Evaluation of the Effect of 6-OH-Dopamine Lesions on Binding Site Labeled with the Cocaine Analog, [125I] RTI-55. NIDA Monograph Series (in press)

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00230-01 CNG

PERIOD COVERED

October 1 1992 to September 30 1993

TITLE OF PROJECT

Effects of Drugs on Physiology, Performance and Mood

PRINCIPAL INVESTIGATOR

P.I.	CR Schuster	Senior Scientist	Office of the Director
	SR Maddox	IRTA	Office of the Director
	CE Johanson	Chief	Etiology Branch
	WR Lange	Clinical Director	Medical Affairs

COOPERATING UNITS

LAB/BRANCH

Office of the Director

SECTION

Office of the Director

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
1	1	0

CHECK APPROPRIATE BOXES

☐ (A) Human ☐ (b) Human Tissue ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

This project is the first of a series of studies to evaluate the conditions under which drugs develop conditioned reinforcing properties. It is thought that these conditioned reinforcing properties are influential in the initiation and maintenance of drug-taking behavior and may also influence the subjective effects experienced by the individual. The first study was designed to determine whether placebo capsules that were associated with high rates of reinforcement producd changes in mood and physiological states. The results showed that subjects preferentially chose to ingest the capsule color associated with high reinforcement and they also reported increases in positive subjective states. In a second study, subjects given exposure to capsules associated with high versus low rates of reinforcement did not report increases in the elation and positive mood scales in the absence of reinforcement. These results indicate that there is a differentiation between conditioning of mood states and drug preference. Future studies are designed to evaluate the process of conditioned reinforcement and the separation of this process and alterations in mood states.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00231-01 CTS

PERIOD COVERED

October 1 1992 to September 30 1993

TITLE OF PROJECT

Evaluation of Pharmacologic Treatments of Opiate and Cocaine Dependence

PRINCIPAL INVESTIGATOR

P.I.	KL Preston	Chief	Treatment Branch
	I Montoya	Visiting Fellow	Treatment Branch
	D Gorelick	Chief	Treatment Branch
	K Silverman	Staff Fellow	Treatment Branch

COOPERATING UNITS

LAB/BRANCH

Treatment Branch

SECTION

Clinical Trials

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
1.85	1.45	0.4

CHECK APPROPRIATE BOXES

☒ (A) Human ☐ (b) Human Tissue ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

This project assesses the safety and efficacy of pharmacological treatments of cocaine and opioid abuse in clinical trials. Findings of a clinical trial recently completed in our section do not support the utility of carbamazepine in the treatment of cocaine dependence. A double-blind, placebo-controlled clinical trial was completed testing carbamazepine in cocaine dependent subjects. Outcome measures were persent cocaine-negative urine samples, self-reported drug use, and self-reported craving for cocaine. There were no significant differences between subjects randomly assigned to the placebo or carbamazepine treatment groups on any of the primary outcome measures. The administration of carbamazepine to cocaine dependent individuals was safe at the dose tested.

Evidence from preclinical studies suggests that the reinforcing effects of cocaine are related to its inhibition of dopamine reuptake. Much of the work to develop pharmacological treatments of cocaine dependence has thus far focused on dopaminergic agents, though no dopaminergic agents have yet been shown to be effective in reducing cocaine use. An open trial testing the safety and efficacy of combination treatment with buproprion and bromocriptine, agents with dopaminergic activity, is underway and has so far shown a low incidence of side effects among treated subjects. This study is the first to apply the strategy of combining pharmacologic agents to increase the efficacy of individual agents in the treatment of cocaine dependence.

The partial opiate agonist buprenorphine is a safe and effective treatment for opiate dependence. Some preclinical studies and uncontrolled clinical case series have suggested that buprenorphine might also be effective in reducing cocaine use by opiate addicts. A double-blind, controlled clinical trial is underway that directly evaluates the efficacy of buprenorphine in reducing both opiate and cocaine use in dually opiate- and cocaine-dependent patients.

Medically supervised withdrawal from opioids is a commonly used treatment but is usually not effective in establishing long-term abstinence because patients frequently relapse soon after completion of the withdrawal. A procedure for initiating naltrexone maintenance during withdrawal treatment is being developed to provide a more effective post-withdrawal treatment. The efficacy of buprenorphine/naltrexone combinations are being tested in a clinical trial.

Preston KL, Bigelow GE. Differential naltrexone antagonism of hydromorphone and pentazocine in human volunteers. Journal of Pharmacology and Experimental Therapeutics 1993; 264:813-823.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00232-01 CTS

PERIOD COVERED

October 1 1992 to September 30 1993

TITLE OF PROJECT

Evaluation of Non-Pharmacological Treatments of Substance Abuse

PRINCIPAL INVESTIGATOR

PI	KL Preston	Chief	Treatment Branch
	L Covi	Visiting Scientist	Treatment Branch
	K Silverman	Staff Fellow	Treatment Branch
	I Montoya	Visiting Fellow	Treatment Branch
	CR Schuster	Senior Scientist	Office of the Director

COOPERATING UNITS

LAB/BRANCH

Treatment Branch

SECTION

Clinical Trials

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD

TOTAL STAFF YEARS	PROFESSIONAL	OTHER
2	1.6	0.4

CHECK APPROPRIATE BOXES

☒ (a) Human ☐ (b) Human Tissue ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

Two major projects were completed this year in which non-pharmacological treatments of substance abuse were tested. In the first project, a behavioral intervention, contingency management, was used to treat cocaine use among a group of methadone maintenance patients. In the second project the effects of intensity of counseling in cocaine dependence was evaluated.

The effectiveness of contingency management procedures designed to produce sustained cocaine abstinence was evaluated in opioid-dependent cocaine abusers participating in a methadone maintenance program. Thirty-seven methadone maintenance subjects who used cocaine regularly during a 5-week baseline period were randomly assigned to either a contingency management group or to a yoked control group. Subjects in the contingency management group earned vouchers (exchangeable for goods or services) for providing cocaine-free urine samples (i.e., samples negative for benzoylecgonine); the value of the vouchers increased as the number of consecutive cocaine-free urine samples increased. Subjects in the yoked control group received vouchers of comparable value and at approximately the same frequency as subjects in the contingency management condition, but independent of the presence or absence of cocaine-free urines. Preliminary results indicate that the persons in the contingency management group achieved substantially longer periods of sustained abstinence from cocaine use than persons in the yoked control group.

Counseling is an important element of virtually all drug abuse treatment; thus standardization and evaluation of counseling procedures is needed to establish effective treatment, whether counseling is the sole treatment or is given in combination with pharmacotherapy. A 12-week study was recently completed in which the efficacy of a standardized individual Cognitive/Behavioral/Interpersonal counseling program administered according to a specified therapy manual, given either twice weekly, once weekly, or every two weeks, were compared. Outcome measures included cocaine and other drug use (by self-report and urine toxicology), cocaine craving, psychological state, and psychosocial functioning. Preliminary analysis indicated that there were fewer initial drop-outs in the twice a week treatment group, but no significant differences in drug use outcome measures between groups after twelve weeks of treatment. The manual is currently being adapted for use in a group treatment format.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00233-01 CTS

PERIOD COVERED

October 1 1992 to September 30 1993

TITLE OF PROJECT

Development of Methods for Screening Pharmacologic Treatments of Substance Abuse

PRINCIPAL INVESTIGATOR

P.I.	KL Preston	Chief	Treatment Branch
	K Silverman	Staff Fellow	Treatment Branch
	I Montoya	Visiting Fellow	Treatment Branch
	T Llosa	Visiting Fellow	Treatment Branch

COOPERATING UNITS

LAB/BRANCH

Treatment Branch

SECTION

Clinical Trials

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
0.9	0.7	0.2

CHECK APPROPRIATE BOXES

☒ (A) Human ☐ (b) Human Tissue ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

We have begun a program of research to develop a laboratory model of cocaine abuse using very low doses of oral cocaine, doses that produce measurable behavioral effects but minimal cardiovascular effects. The first protocol in this research program uses a drug discrimination procedure to explore the limits of human behavioral sensitivity to oral cocaine. Initially, subjects in this protocol are taught to distinguish 50 mg of oral cocaine from placebo using a drug discrimination procedure. Then subjects are exposed to 4 doses of oral cocaine (6.25 mg, 12.5 mg, 25 mg, and 50 mg) and placebo in random order across days to determine the lowest doses of cocaine that subjects can detect. Throughout all of these administrations the cardiovascular and self-reported mood effects of these cocaine doses are determined. The protocol is currently ongoing. Further studies are planned to study cocaine and opioid drug discrimination, cocaine and opioid self-administration studies, and the pharmacodynamic and pharmacokinetic effectsot coca tea.

Sullivan JT, Preston KL, Testa MP, Busch M, Jasinski DR. Evaluation of the psychoactivity and abuse liability of the 5-HT1D agonist sumatriptan. Clinical Pharmacology and Therapeutics 1992; 52:635-642.

Silverman K, Evans SM, Strain EC, Griffiths RR. Withdrawal syndrome after the double-blind cessation of caffeine consumption. The New England Journal of Medicine 1992; 327:1109-1114.

Silverman K, Evans SM, Strain EC, Griffiths RR. Syndrome de sevrage après arrêt en double-aveugle de la consommation de caféine. Le Journal International de Medécine 1992; 252:26-32. (Reprinted from NEJM, 327, 1109-
1114)

Griffiths RR, Troisi JR, Silverman K, Mumford GK. The multiple-choice procedure: An efficient method for investigating drug reinforcement. Behavioural Pharmacology 1993; 4:3-13.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00234-01 CTS

PERIOD COVERED

October 1 1992 to September 30 1993

TITLE OF PROJECT

Assessment of Psychological Issues Related to Substance Abuse Treatment

PRINCIPAL INVESTIGATOR

P.I.	KL Preston	Chief	Treatment Branch
	L Covi	Visiting Scientist	Treatment Branch
	I Montoya	Visiting Fellow	Treatment Branch
	T Llosa	Visiting Fellow	Treatment Branch
	A Andrade	Guest Worker	Treatment Branch

COOPERATING UNITS

LAB/BRANCH

Treatment Branch

SECTION

Clinical Trials

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
0.55	0.45	0.1

CHECK APPROPRIATE BOXES

☒ (A) Human ☐ (b) Human Tissue ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

The psychological assessment of subjects participating in clinical trials has become an important part of the section's research interest. A study of psychopathology and cognitive functions by drug dependence diagnosis completed in the past year showed that cocaine-dependent subjects seeking treatment have higher psychopathology scores and better cognitive function levels than heroin-dependent subjects seeking treatment. In another study we demonstrated that participation of drug abusing subjects in residential, non-treatment studies is psychologically safe and has a beneficial effect on psychological symptoms.

Seasonal variation in drug abuse was noted from Lexinton ARC admission data. Anecdotally violence, particularly riots, in prison also show seasonal variation. Since dual diagnosis of antisocial personality and drug abuse is very common, there may be a temporal relationship between drug abuse and other antisocial behaviors. High security prisons offer a population presumably vulnerable to drug abuse in an environment with a low availability of abusable substances. The discipline records from a 45 month period for a large number of prisoners were studied. An increased number of disciplinary infractions was found in the summer months, though wide variability occurred over the period studied. These data suggest the need for further research in the seasonal relationship between drug abuse and violence.

A number of psychological assessment tools are being developed and evaluated. Preliminary results from a newly developed Dream Assessment Questionnaire showed that drug dreams are frequently reported among drug abusers seeking treatment and their characteristics were described. Spirituality is an important element in some drug abuse treatment programs; evaluations of the degree and changes in spirituality among treatment patients are being initiated. The concept of drug craving is an important aspect of drug use behavior. For example, craving is considered a factor in the maintenance of drug use and in relapse during treatment or following abstinence and has been used as a surrogate measure for drug use in clinical trials. Craving reduction has also been the target of initiatives to develop efficacious medications for treating drug abuse and dependence. An evaluation of a newly developed Craving Questionnaire is being planned. Other areas under study include the relationships between substance abuse and sociodemographic factors, personality disorders, and psychiatric co-morbidity.

rtzen CA, Covi L, Buxton K, Richards H. Seasonal changes in rule infractions among prisoners: A minary test of the temperature-aggression hypothesis. Psychological Record 1993; 72:195-200.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00235-01 CDM

PERIOD COVERED

October 1 1992 to September 30 1993

TITLE OF PROJECT

Detection of Drugs of Abuse in Human Sweat

PRINCIPAL INVESTIGATOR

P.I.	EJ Cone	Chief	Clinical Pharmacology Branch
	WD Darwin	Chemist	Clinical Pharmacology Branch
	A Jenkins	Staff Fellow	Clinical Pharmacology Branch

COOPERATING UNITS

LAB/BRANCH

Clinical Pharmacology Branch

SECTION

Chemistry

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
0.4	0.1	0.3

CHECK APPROPRIATE BOXES

☒ (A) Human ☐ (b) Human Tissue ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

Sweat was evaluated as a media for use in monitoring drug exposure of human subjects. Healthy subjects with a history of chemical substance abuse volunteered for these studies. Informed consent was obtained and all procedures were approved by the hospital Institutional Review Board. Following the administration of cocaine, marijuana or opiates, sweat samples were collected periodically. Other biological specimens like saliva, blood, urine and hair also were collected. Specimens were analyzed by immunoassay and gas chromatography/mass spectrometry.

These data will provide new information on this unusual biological specimen which may be useful in development of methods for monitoring human drug exposure.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00236-01 NDAS

PERIOD COVERED

October 1 1992 to September 30 1993

TITLE OF PROJECT

Opioids and Organ Preservation

PRINCIPAL INVESTIGATOR

P.I. TP Su Research Chemist Neuroscience Branch

COOPERATING UNITS

LAB/BRANCH

Neuroscience Branch

SECTION

Neuroimaging and Drug Action

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
0.1	0.1	0

CHECK APPROPRIATE BOXES

☐ (A) Human ☐ (b) Human Tissue ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

DADLE and DPDPE, a peptide more selective than DADLE at the delta opioid receptor, markedly prolong the organ survival time in a canine multiorgan preparation. Results of a preliminary transplantation experiment indicate that the recipient dog functions normally after receiving a lung preserved over 40 h with DADLE in the multiorgan preparation.

n S, PR Oeltgen, JN Diana, RK Salley and T-P Su (1993): Extension of tissue survival time in multiorgan preparation using a delta opioid DADLE. J. Thorac. Cardiovasc. Surg., in press.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00237-01 NDAS

PERIOD COVERED

October 1 1992 to September 30 1993

TITLE OF PROJECT

Ligand Development and Imaging Studies of Sigma Receptors

PRINCIPAL INVESTIGATOR

P.I.	ED London	Chief	Neuroscience Branch
	K Hashimoto	Visiting Fellow	Neuroscience Branch
	AS Kimes	Biologist	Neuroscience Branch

COOPERATING UNITS

LAB/BRANCH

Neuroscience Branch

SECTION

Neuroimaging and Drug Action

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
1.05	1.05	0

CHECK APPROPRIATE BOXES

☐ (A) Human ☐ (b) Human Tissue ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

@This project includes studies of potential ligands for imaging sigma receptors using autoradiography, positron emission tomography (PET) or single photon emission tomography (SPECT). Studies of cerebral metabolism in rats show that d-N-allylnormetazocine, a sigma receptor ligand produces dose-dependent effects, reflecting affinities of the drug for sigma and phencyclidine receptors. This study provides experimental evidence that sigma receptors are linked to functional receptors in brain. Radiolabeled 1-(p-iodophenyl)-3-(1-adamantyl)guanidine (PIPAG) binds selectively and with high affinity to sigma receptors in guinea-pig cerebral membranes. Autoradiographically assayed PIPAG binding in slices of guinea-pig brain parallels that of other sigma ligands, suggesting that further study of this potential SPECT ligand is warranted. Sigma receptors are characterized as sigma-1 or sigma-2 receptors based on the relative potencies of known sigma ligands to compete for binding sites in receptor binding assays. Radiolabeled ifenprodil may label selectively sigma-2 receptors in rat brain at 37 degrees C, as the pharmacological profile of ifenprodil binding is highly correlated with that of sigma-2, but not sigma-1 receptors. A new ligand for in vivo and in vitro labeling of sigma receptors, 4-PPBP, is being developed.

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nimoto K and ED London (1993): Further characterization of [3H]ifenprodil binding to * receptors in rat n. Eur. J. Pharmacol. 236:159-163.

don ED and SR Zukin (1993): Sigma receptors, PCP receptors and the developing nervous system. In: eptors in the Developing Nervous System, Volume 2: Neurotransmitters, IS Zagon, PJ McLaughlin, eds., oman & Hall, London, pp 215-230.

es AS, AA Wilson, U Scheffel, BG Campbell and ED London (1992): Radiosynthesis, cerebral distribution binding of [125I]1-(p-iodophenyl-3-(1-adamantyl)guanidine ([125I]PIPAG), a sigma receptor ligand. J. Med. m.. 35:4683-4689.

nimoto K and ED London (1993) Imaging * receptors and cerebral responses to * drugs. In: Sigma eptors, Y. Itzhak, ed., Academic Press, London, in press.

Puppa A, AS Kimes, and ED London (1993): Dose-dependent effects of d-N-allylnormetazocine on onal cerebral metabolic rates for glucose. Brain Res. 603:38-46

nimoto K, CR Mantione, MR Spada, JL Neumeyer, and ED London (1933): Further characterization of fenprodil in rat brain. Eur. J. Pharmacol., in press

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00238-01 NDAS

PERIOD COVERED

October 1 1992 to September 30 1993

TITLE OF PROJECT

Bioassay, A Statistical Analysis Program

PRINCIPAL INVESTIGATOR

P.I. DB Vaupel Pharmacologist Neuroscience Branch

COOPERATING UNITS

J Katz, Psychobiology Section

LAB/BRANCH

Neuroscience Branch

SECTION

Neuroimaging and Drug Action

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
0.1	0.1	0

CHECK APPROPRIATE BOXES

☐ (A) Human ☐ (b) Human Tissue ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

@A statistical analysis program entitled BIOASSAY is being written for parallel line bioassays, linear regression analysis, Dunnett's test and missing value analyses. This program is being developed specifically to make more efficient use of balanced experimental designs for human and primate pharmacological studies. The statistical advantages of the program include: the calculation of relative potency estimates and confidence limits without using statistical shortcuts; integrating a Between Subjects or Animals variance component with parallel line, linear regression and Dunnett's tests; incorporating a missing values routine for randomized block experimental designs; and having the capability of making inverse predictions with confidence limits from linear dose-response curves. The project involves providing statistical models to the programmers and validating the resulting software. The program is being written in C for use with DOS systems by Ogden Bioservices, through a professional services contract.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00239-01 BPGS

PERIOD COVERED

October 1 1992 to September 30 1993

TITLE OF PROJECT

Peripheral Mechanisms of Opioid Analgesia

PRINCIPAL INVESTIGATOR

P.I.	SR Goldberg	Chief	Preclinical Pharmacology Laboratory
	C Stein	Guest Worker	Preclinical Pharmacology Laboratory
	M Schaefer	Visiting Fellow	Preclinical Pharmacology Laboratory
	L Carter	Guest Worker	Preclinical Pharmacology Laboratory
	S Mousa	Guest Worker	Preclinical Pharmacology Laboratory

COOPERATING UNITS

Dept of Anesthesiology, Johns Hopkins University

LAB/BRANCH

Preclinical Pharmacology Laboratory

SECTION

Behavioral Pharmacology

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
3.6	1.6	2

CHECK APPROPRIATE BOXES

☐ (A) Human ☐ (b) Human Tissue ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

With regard to their analgesic effects, opioids have been thought to act on receptors within the central nervous system exclusively. Recently, however, we have shown that, within inflamed rat paws, immune-cell derived opioid peptides can activate peripheral opioid receptors located on sensory nerves and induce antinociception. The purpose of our current research is to examine agents for their capability of releasing opioid peptides from immune cells and for their potential in the inhibition of pain. Such peripheral effects are of considerable interest in view of the avoidance of centrally mediated side effects of opioid analgesics, such as dysphoria, dependence, addiction, sedation and respiratory depression. Our most recent experiments have examined whether corticotropin releasing factor (CRF) or interleukin-1Beta (IL-1Beta) release opioid peptides in inflamed tissue and result in analgesia. Upon administration of CRF or IL-1Beta into both paws of rats with unilateral hindpaw inflammation, nociceptive thresholds increase markedly in the inflamed but not in the noninflamed paw. Alpha-helical-CRF and interleukin-1 receptor antagonist, respectively, antagonize this analgesic effect, indicating that CRF and IL-1Beta act via their specific receptors. These receptors are most likely localized on immune cells within the inflamed tissue because immunosuppression by cyclosporin A attenuates the effect. In experiments with antisera against opioid peptides we have shown that endogenous opioids released from immune cells mediate these analgesic effects. This is supported by the fact that naloxone and other opioid antagonists reverse these effects. These results suggest that CRF and IL-1Beta, by activation of their receptors on immune cells, cause a release of opioids which subsequently occupy their receptors on sensory nerves resulting in inhibition of pain. Ongoing in vitro experiments examine whether CRF or IL-1Beta are capable of releasing endorphin in cell suspensions prepared from inflamed and noninflamed lymph nodes and whether this release can be attenuated by the respective antagonists. To further elucidate the mechanisms governing the apparent "upregulation" of opioid receptors on sensory nerves during inflammation, we are examining the permeability of the perineurial barrier by histochemistry.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00240-01 PTS

PERIOD COVERED

October 1 1992 to September 30 1993

TITLE OF PROJECT

Development of New Pharmacologic and Biologic Treatment for Drug Dependence

PRINCIPAL INVESTIGATOR

P.I.	DA Gorelick	Chief	Treatment Branch
	L Weinhold	Staff Fellow	Treatment Branch
	L Cheskin	Senior Staff Fellow	Treatment Branch

COOPERATING UNITS

Clinical Pharmacology Branch
Preclinical Pharmacology Branch

LAB/BRANCH

Treatment Branch

SECTION

Pharmacotherapy

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
1.9	1.5	0.4

CHECK APPROPRIATE BOXES

☒ (A) Human ☐ (b) Human Tissue ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

This project assesses the efficacy and safety of new pharmacologic and biologic treatments for drug dependence using experimental paradigms in a controlled, residential environment. Some animal and open-label human studies suggest that the anti-convulsant carbamazepine may reduce cocaine craving and use, possibly by blocking the development of cocaine-induced kindling. However, a recently completed double-blind study did not support the efficacy of carbamazepine in the treatment of cocaine dependence.

In humans, very low calorie diets producing ketonemia are associated with the absence of hunger, but it is not known whether this subjective effect also applies to drugs of abuse. In animals, balanced low calorie diets not producing ketonemia increase drug self-administration. A second component of this project is evaluating which of these dietary effects operates in human drug abusers, using nicotine (cigarette smoking) as the target drug. Preliminary results indicate that a balanced low calorie diet increases cigarette smoking, while a low calorie ketogenic diet does not alter smoking. These findings have clinical implications, especially since some drugs of abuse themselves suppress appetite and thus may produce calorie deprivation.

The primary enzyme metabolizing cocaine in humans is butyrylcholinesterase. In theory, alterations in enzyme activity might alter brain levels of cocaine and its metabolites and thus alter cocaine's effects, with possible therapeutic benefits. In a collaborative study with the Preclinical Pharmacology Laboratory and the National Institute on Aging, compounds which alter butyrylcolinesterase activity are given to monkeys to determine whether they alter the acute effects of cocaine.

Weinhold, L.L., Preston, K.L., Farre', M., Liebson, I.A., and Bigelow, G.E. (1992). Buprenorphine alone and in combination with naloxone in non-dependent humans. Drug and Alcohol Dependence, Vol. 30, 263-274.

Weinhold, L.L., Jaffe, A.B., Sharpe, L.G. Pinning behavior in rats before and after sufentanil self-administration. BPharmacology, Biochemistry and Behavior, in press.

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Gorelick DA: Medications for the treatment of substance abuse. Current Opinion in Psychiatry 5:430-435, 1992.

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Gorelick DA: Recent developments in pharmacological treatment of alcoholism. In Galanter, M (ED), Recent Developments in Alcoholism,
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Newlin DB, Wong CJ, Cheskin LJ. Cardiovascular responses to naloxone challenge in opiate-dependent individuals. Pharmacology, Biochemistry & Behavior, 43 (2):357-360, 1992.

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Moscatello S, Cheskin LJ, Irritable bowel syndrome. J Am Osteopathic Assoc., in press.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00241-01 PTS

PERIOD COVERED

October 1 1992 to September 30 1993

TITLE OF PROJECT

Identification of Factors Associated with Response to Drugs and Treatment

PRINCIPAL INVESTIGATOR

P.I.	DA Gorelick	Chief	Treatment Branch
	L Weinhold	Staff Fellow	Treatment Branch
	I Montoya	Visiting Fellow	Treatment Branch

COOPERATING UNITS

Molecular Neurobiology Branch

LAB/BRANCH

Treatment Branch

SECTION

Pharmacotherapy

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
0.9	0.6	0.3

CHECK APPROPRIATE BOXES

☒ (A) Human ☐ (b) Human Tissue ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

Drug abusers vary widely in their acute and chronic responses to drugs and in their compliance with and response to drug abuse treatment. A better understanding of the factors associated with individual differences in response should result in the development of more effective and efficient treatment interventions. This project assesses several biological and psychosocial characteristics of drug abusers and correlates them with abusers' response to their abused drug or to the abusers' treatment compliance and outcome.

One component, in collaboration with Dr. Raymond Woosley, Department of Pharmacology, Georgetown University, measures activity of the plasma enzyme butyrylcholinesterase, the main cocaine-metabolizing enzyme in humans. Preliminary results indicate that cocaine addicts tend to have normal enzyme activity, which can vary four-fold between addicts. A second component assesses psychiatric co-morbidity, personality traits, mood, neuropsychological function, and social demographic characteristics in drug abusers using structured and semi-structured diagnostic interviews and computer-administered psychological tests. A third component, in collaboration with Dr. James Frost, Department of Radiology, Johns Hopkins University, uses positron emission tomography (PET) scanning to evaluate the effect of chronic cocaine abuse on mu-opiate receptor function in the brain, and the relationship between such receptor function and the severity and time course of cocaine withdrawal. Another component, in collaboration with the Molecular Neurobiology Laboratory, assesses various neurotransmitter-associated genotypes with the goal of identifying alleles significantly associated with particular substance use disorders.

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abusers. Archives of General Psychiatry 49:723-727, 1992.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00242-01 PTS

PERIOD COVERED

October 1 1992 to September 30 1993

TITLE OF PROJECT

Prevention or Amelioration of Biomedical Consequences of Drug Abuse

PRINCIPAL INVESTIGATOR

P.I.	DA Gorelick	Chief	Treatment Branch
	L Weinhold	Staff Fellow	Treatment Branch

COOPERATING UNITS

LAB/BRANCH

Treatment Branch

SECTION

Pharmacotherapy

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
0.5	0.3	0.2

CHECK APPROPRIATE BOXES

☒ (A) Human ☐ (b) Human Tissue ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

Drug abuse has serious, often lethal, biomedical consequences, such as HIV infection and cardiovascular dysfunction. This project studies subject characteristics, high-risk behaviors, and other factors associated with such consequences, with the goal of developing interventions to prevent or ameliorate them. One study currently underway provides a comprehensive, non-invasive assessment of cardiovascular function in cocaine abusers, using 24-hour ambulatory monitoring of EKG, blood pressure, and heart rate; high-resolution EKG; analysis of heart rate variability (vagal tone), and echocardiography. Evaluation of the subclinical effects of acute and chronic cocaine use on cardiovascular function will help elucidate the mechanisms of cocaine's cardiovascular effects, hopefully leading to their prevention or amelioration.

Tashkin DP, Khalsa M-E, Gorelick D, Chang P, Simmons MS, Coulson AH, & Gong Jr H: Pulmonary status of habitual cocaine smokers.. American Review of Respiratory Disease 145:92-100. 1992.

Soderstrom, CA, Dischinger, PC, Smith, GS, McDuff, DR, Hebel, JR, & Gorelick, DA: Psychoactive substance dependence among trauma center patients. Journal of the American Medical Association 267:2756-2759, 1992.

Gorelick DA: Pathophysiological effects of cocaine in humans: Review of scientific issues. Journal of Addictive Diseases, 11 (no. 4):97-110, 1992.

Tashkin DP, Gorelick D, Khalsa M-E, Simmons M, & Chang P: Respiratory effects of cocaine freebasing among habitual cocaine users. Journal of Addictive Diseases. 11(no. 4):59-70, 1992.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00243-01 PTS

PERIOD COVERED

October 1 1992 to September 30 1993

TITLE OF PROJECT

Development of Human Experimental Methods for Evaluating Drug Abuse Therapy

PRINCIPAL INVESTIGATOR

P.I.	DA Gorelick	Chief	Treatment Branch
	L Weinhold	Staff Fellow	Treatment Branch

COOPERATING UNITS

Clinical Pharmacology Branch

LAB/BRANCH

Treatment Branch

SECTION

Pharmacotherapy

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
0.4	0.3	0.1

CHECK APPROPRIATE BOXES

☒ (A) Human ☐ (b) Human Tissue ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

Most existing methods for evaluating the efficacy and safety of pharmacotherapies for drug abuse involve either the time and expense of clinical treatment trials or short-term experimental models which have the medical risk of drug administration and whose relevance to clinical drug abuse may be questionable. The goal of this project is to develop human experimental methods in a controlled residential research ward environment which can safely and efficiently be used to evaluate potential treatment medications. One study has used a drug self-administration paradigm analogous to those used in animal research, in which human subjects could make a stimulus-controlled operant response to earn an iv injection of low-dose cocaine or saline. Results showed that cocaine abusers could distinguish cocaine from saline injections and found the former highly reinforcing and the latter non-reinforcing. Data from the study are being analyzed to evaluate the relationship between drug self-administration and craving for cocaine, since the latter is often used as a surrogate outcome variable in studies of drug abuse treatment. Two different methods for measuring cocaine craving, visual-analogue scales and Likert scales, are also being evaluated.

Another component is studying conditioned or context-specific behavioral sensitization as a method for evaluating clinically relevant effects of cocaine. While this phenomenon has been demonstrated in animals, it has never been demonstrated in humans.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00244-01 PTS

PERIOD COVERED

October 1 1992 to September 30 1993

TITLE OF PROJECT

Evaluation of Existing Treatments for Drug Abuse

PRINCIPAL INVESTIGATOR

P.I.	J Ball	Visiting Scientist	Treatment Branch
	S Greberman	IRTA	Treatment Branch
	DA Gorelick	Chief	Treatment Branch

COOPERATING UNITS

LAB/BRANCH

Treatment Branch

SECTION

Pharmacotherapy

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
2.05	2	0.05

CHECK APPROPRIATE BOXES

☒ (A) Human ☐ (b) Human Tissue ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

Existing treatments for drug abuse often show wide variations in effectiveness, both across treatment programs and across patients. A better understanding of the factors contributing to such variations could lead to identification and implementation of changes that promote increased treatment effectiveness. This project, conducted by the Drug Abuse Treatment Evaluation Unit headed by Dr. John Ball, applies a comprehensive schema for evaluating drug abuse treatment programs in four areas: patient history and characteristics, program characteristics, treatment services provided, and treatment outcome. Current studies are (1) evaluating the validity of information self-reported by opiate addicts, e.g., criminal behavior; (2) applying time series analysis to the evaluation of outcomes of methadone maintenance treatment, and (3) evaluating the effect of prior drug abuse treatment on the outcome of short-term inpatient detoxification.

Another component of this project is evaluating factors associated with drug users seeking treatment in a hospital mergence room. Drug users may present to a hospital emergency room for a variety of reasons, some clinically appropriate (e.g., a life-threatening medical consequence of drug use) and some less efficient uses of the health care system (e.g., non-urgent medical condition, attempt to enter substance abuse treatment). There is little data available on the relationship between emergency room visits by drug users and their seeking of and participation in drug abuse treatment. This study, in collaboration with the Department of Emergency Medicine at the Francis Scott Key Medical Center, Baltimore, MD, collects data on the sociodemographic, drug use, and treatment-seeking behavior of an unselected series of drug users visiting an urban hospital emergency room.

Ball, J.C. "Comprehensive Outcome Evaluation of Methadone Maintenance Programs in the United States." In: Peter Vamos & Paul Corriveau Drugs and Society to the Year 200: Proceedings of the XIV World Conference of Therapeutic Communities, Chapter 13, vol. 2:1226-1236, 1992.

Ball, J.C. "Why Has It Proved So Difficult to Match Drug Abuse Patients To Appropriate Treatment?" Addiction, in press.

Ball, J.C. and Wijngaart, G.F. "Methadone Maintenance Treatment: Harm Reduction or Rehabilitation?" Addiction, in press.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00245-01 BDS

PERIOD COVERED

October 1 1992 to September 30 1993

TITLE OF PROJECT

Smoked Drugs: Mechanisms of Reinforcement

PRINCIPAL INVESTIGATOR

P.I.	JE Henningfield	Chief	Clinical Pharmacology Branch
	SJ Heishman	Research Psychologist	Clinical Pharmacology Branch
	WI Pickworth	Research Psychologist	Clinical Pharmacology Branch
	RM Keenan	Guest Worker	Clinical Pharmacology Branch
	LM Scwandt	IRTA	Clinical Pharmacology Branch
	SM Evans	Staff Fellow	Clinical Pharmacology Branch

COOPERATING UNITS

Chemistry and Drug Metabolism Section

LAB/BRANCH

Clinical Pharmacology Branch

SECTION

Biology of Dependence

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
1	0.5	0.5

CHECK APPROPRIATE BOXES

☒ (A) Human ☐ (b) Human Tissue ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

The mechanisms by which drugs affect human behavior are complex and not well understood. The ultimate effects of a drug will depend on the interaction between the drug dose, the person's physiological and psychological state, the particular environmental conditions, and the nature of the behavior or test being measured. One approach that we are pursuing is to vary the environmental conditions by manipulating the reinforcement (monetary) contingencies under which subjects perform various tasks. This can be thought of as manipulating a subject's motivation to perform. By also varying drug dose and using tests that measure different aspects of performance (e.g., psychomotor vs. cognitive), we can begin to explore the complex interactions underlying the effects of drugs on behavior.

Another approach to investigating the mechanisms by which drugs influence behavior is to focus on performance impairment produced by psychoactive drugs. The performance-impairing effects of drugs of abuse produce a large toll on the nation each year in terms of traffic injuries and fatalities and lost productivity in the workplace. However, for most drugs, we lack basic knowledge about the behavioral mechanisms underlying their impairment of human performance. A series of studies is being conducted that will address such questions. A battery of physiological, behavioral, and performance measures designed to determine whether an individual is behaviorally impaired as the result of taking a drug has been tested with ethanol, marijuana, and cocaine. A future study will examine the effects of amphetamine, codeine, and alprazolam on this same test battery as well as a cognitive test of attention and memory. By also collecting blood samples during these studies, we will be able to gain valuable information concerning the relationship between plasma concentrations of drugs and degree of performance impairment.

enningfield, J.E., Stapleton, J.M., Benowitz, N.L., Grayson, R.F. and London, E.D. Higher levels of nicotine in terial than in venous blood after cigarette smoking. Drug and Alcohol Dependendence, 33:23-29, 1993.

enningfield, J.E. and Keenan, R.M. Nicotine delivery system determines kinetics and abuse liability. Journal Consulting and Clinical Psychology, in press.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00246-01 BDS

PERIOD COVERED

October 1 1992 to September 30 1993

TITLE OF PROJECT

Determinants of Drug Abuse Liability

PRINCIPAL INVESTIGATOR

P.I.	SJ Heishman	Research Psychologist	Clinical Pharmacology Branch
	JE Henningfield	Chief	Clinical Pharmacology Branch
	CR Schuster	Senior Scientist	Office of the Director
	LM Schwandt	IRTA	Clinical Pharmacology Branch
	SM Evans	Staff Fellow	Clinical Pharmacology Branch

COOPERATING UNITS

LAB/BRANCH

Clinical Pharmacology Branch

SECTION

Biology of Dependence

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
2	1	1

CHECK APPROPRIATE BOXES

☒ (A) Human ☐ (b) Human Tissue ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

Psychoactive substances vary considerably in their abuse liability from those such as major tranquilizers in which self-administration is difficult to sustain to smokable forms of cocaine which are highly addictive. Quantitation of the differences and discovering the mechanisms which underly the differences is fundamental to the development of safer medications in general, as well as for the development of more effective medications for treating addiction. Two strategies for human evaluation of the mechanisms of drug abuse liability are drug discrimination and drug self-administration. Both of these paradigms evolved from animal research and their application to humans makes it possible to apply animal and human data to identify mechanisms of addiction.

Presently we are using the drug discrimination paradigm to explore the mechanisms which confer a high abuse liabilty upon stimulants such as amphetamine, whereas stimulants such as caffeine are of substantially lower abuse liability. In a series of three studies, the subjective and discriminative effects of several stimulant drugs are being investigated that are widely sold via mail order and designed to imitate amphetamine-like stimulants. These so called "look-alike" stimulants contain caffeine alone or combined with one or more sympathomimetic amines, such as ephedrine and phenylpropanolamine (PPA). Little is known about the behavioral pharmacology in humans of the combined effects of these drugs, including effects when individuals exceed the therapeutic dosage in an attempt to achieve amphetamine-like euphoria. These studies, which are in progress, are investigating the drugs both singly and in combination.

Another series of studies, in progress, is aimed at refining the drug self-administration paradigm presently used to enable more systematic evaluation of the reinforcing effects of opioids. This study of opioid self-admininistration will then be extended to evaluate the role of behavioral factors as modulators of the reinforcing effects of the drugs.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00247-01 BDS

PERIOD COVERED

October 1 1992 to September 30 1993

TITLE OF PROJECT

Behavioral Mechanisms of Drug Effects

PRINCIPAL INVESTIGATOR

P.I.	SJ Heishman	Research Psychologist	Clinical Pharmacology Branch
	JE Henningfield	Chief	Clinical Pharmacology Branch
	RC Taylor	Research Psychologist	Clinical Pharmacology Branch

COOPERATING UNITS

LAB/BRANCH

Clinical Pharmacology Branch

SECTION

Biology of Dependence

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
1	0.5	0.5

CHECK APPROPRIATE BOXES

☒ (A) Human ☐ (b) Human Tissue ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

The mechanisms by which drugs affect human behavior are complex, involving the interaction between the direct actions of the drug (e.g., impairment of coordination) and the functional behavioral effects such as altered motivation. Specific determinants of drug response include the drug dose, the route of administration, the person's physiological and psychological state, the particular environmental conditions, and the nature of the behavior or test being measured. One approach that we are pursuing is to vary the environmental conditions by manipulating the reinforcement (monetary) contingencies under which subjects perform various tasks. This can be thought of as manipulating a subject's motivation to perform. By also varying drug dose and using tests that measure different aspects of performance (e.g., psychomotor vs. cognitive), we can begin to explore the complex interactions underlying the effects of drugs on behavior.

Another approach to investigating the mechanisms by which drugs influence behavior is to focus on performance impairment produced by psychoactive drugs. The performance-impairing effects of drugs of abuse produce a large toll on the nation each year in terms of traffic injuries and fatalities and lost productivity in the workplace. However, for most drugs, we lack basic knowledge about the behavioral mechanisms underlying their impairment of human performance. A series of studies is being conducted that will address such questions. A battery of physiological, behavioral, and performance measures designed to determine whether an individual is behaviorally impaired as the result of taking a drug has been tested with ethanol, marijuana, and cocaine. A future study will examine the effects of amphetamine, codeine, and alprazolam on this same test battery as well as a cognitive test of attention and memory. By also collecting blood samples during these studies, we will be able to gain valuable information concerning the relationship between plasma concentrations of drugs and degree of performance impairment.

Heishman, S.J. (in press). Strengths and weaknesses in the application of laboratory performance assessment to workplace settings. In: H.S. Axel & D.J. Crouch (Eds.), Research Methods in Workplace Settings. NIDA Research Monograph. Washington, DC: U.S. Government Printing Office.

Heishman, S.J. (in press). Laboratory performance assessment: Impairing effects of psychoactive drugs. NIDA Research Monograph. Washington, DC: U.S. Government Printing Office.

Heishman, S.J., Snyder, F.R. & Henningfield, J.E. (in press). Performance, subjective, and physiological effects of nicotine in nonsmokers. Drug and Alcohol Dependence.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00248-01 BDS

PERIOD COVERED

October 1 1992 to September 30 1993

TITLE OF PROJECT

Neurophysiologic, Performance and Subjective Effects of Nicotine

PRINCIPAL INVESTIGATOR

P.I.	WB Pickworth	Pharmacologist	Clinical Pharmacology Branch
	JE Henningfield	Chief	Clinical Pharmacology Branch

COOPERATING UNITS

LAB/BRANCH

Clinical Pharmacology Branch

SECTION

Biology of Dependence

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
0.65	0.6	0.05

CHECK APPROPRIATE BOXES

☒ (A) Human ☐ (b) Human Tissue ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

Several clinical studies are underway to explore the cognitive effects and neurophysiologic underpinnings of nicotine withdrawal, as well as the effects of various nicotine dosage forms in reversing these effects. Neurophysiologic data indicate the mechanisms of the effects of nicotine and its withdrawal on neural substrates involved in attention, cognition and memory. For example, the effects of mecamylamine, a centrally acting nicotinic antagonist is studied to determine the contribution of tonic cholinergic mechanisms on the EEG and cognitive tasks in smokers and nonsmokers. The ability of transcranially delivered electrostimulation to alleviate nicotine withdrawal was evaluated in a treatment protocol. The efficacy of transdermally delivered nicotine to diminish signs and symptoms of tobacco spontaneous withdrawal are being further tested in a residential study. The interaction of caffeine and nicotine after overnight abstinence was assessed. Dependent measures for these studies include: Gordon vigilance task (with and without distracters), word memory, PAB (performance) spontaneous EEG, evoked potentials, blood pressure, heart rate (physiologic); withdrawal scales, craving, drug liking, drug identification (subjective). These studies are not only helping us to unravel the mechanisms of nicotine addiction but are also of practical value in the development of more effective medications for treating nicotine dependence and withdrawal.

Cohen, C., Pickworth, W.B., Bunker, E.B. and Henningfield, J.E. Caffeine antagonizes EEG effects of nicotine withdrawal. Pharmacol Biochem Behav 1993 (in press).

Cohen, C., Pickworth, W.B. and Henningfield, J.E. Pharmacologic characteristics of tobacco dependence. In: Prevention of Respiratory Disease, Hirsch et al (eds) 1993, pp. 545-558.

Henningfield, J.E., Cohen, C. and Pickworth, W.B. Psychopharmacology of nicotine. In: Nicotine Dependence. J. Slade (ed.) 1993, in press.

Pickworth, W.B., Keenan, R.M. and Henningfield, J.E. Nicotine: Effects and mechanisms. In: Handbook of Neurotoxicology, Vol. 2 Chang and Dyer (eds) 1993, in press.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00249-01 BDS

PERIOD COVERED

October 1 1992 to September 30 1993

TITLE OF PROJECT

Addiction Research Center Inventory Multilingual Versions

PRINCIPAL INVESTIGATOR

P.I.	EG Singleton	Senior Staff Fellow	Clinical Pharmacology Branch
	JE Henningfield	Chief	Clinical Pharmacology Branch
	M Li	Visiting Scientist	Clinical Pharmacology Branch

COOPERATING UNITS

LAB/BRANCH

Clinical Pharmacology Branch

SECTION

Biology of Dependence

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
0.4	0.2	0.2

CHECK APPROPRIATE BOXES

☒ (A) Human ☐ (b) Human Tissue ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

The most widely used instrument to quantitate the psychological effects of drugs of abuse and characterize their addictive potential is the ARC Inventory, but little cross-cultural work has been attempted with the instrument. A Spanish version was developed by investigators in Barcelona, and a Chinese version was developed in collaboration with investigators in Bejing. Preliminary studies have been conducted with each and the data are undergoing evaluation. The Spanish version is being evaluated to assess this translation's relevance to literate and Spanish speaking adults in the United States. The sample was composed of adults from Houston, Texas with a reported history of polysubstance abuse. Each had at least a seventh grade reading level and was literate in the Standard Spanish language as written in Texas. The Chinese version has been given an initial test in China by our collaborators. Analysis of the data from these studies is presently underway.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00250-01 BDS

PERIOD COVERED

October 1 1992 to September 30 1993

TITLE OF PROJECT

Determinants of Drug Abuse Liability

PRINCIPAL INVESTIGATOR

P.I.	SJ Heishman	Research Psychologist	Clinical Pharmacology Branch
	JE Henningfield	Chief	Clinical Pharmacology Branch
	CR Schuster	Senior Scientist	Office of the Director
	LM Schwandt	IRTA	Clinical Pharmacology Branch
	SM Evans	Staff Fellow	Clinical Pharmacology Branch

COOPERATING UNITS

LAB/BRANCH

Clinical Pharmacology Branch

SECTION

Biology of Dependence

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
2	1	1

CHECK APPROPRIATE BOXES

☒ (A) Human ☐ (b) Human Tissue ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

Psychoactive substances vary considerably in their abuse liability from those such as major tranquilizers in which self-administration is difficult to sustain to smokable forms of cocaine which are highly addictive. Quantitation of the differences and discovering the mechanisms which underly the differences is fundamental to the development of safer medications in general, as well as for the development of more effective medications for treating addiction. Two strategies for human evaluation of the mechanisms of drug abuse liability are drug discrimination and drug self-administration. Both of these paradigms evolved from animal research and their application to humans makes it possible to apply animal and human data to identify mechanisms of addiction.

Presently we are using the drug discrimination paradigm to explore the mechanisms which confer a high abuse liabilty upon stimulants such as amphetamine, whereas stimulants such as caffeine are of substantially lower abuse liability. In a series of three studies, the subjective and discriminative effects of several stimulant drugs are being investigated that are widely sold via mail order and designed to imitate amphetamine-like stimulants. These so called "look-alike" stimulants contain caffeine alone or combined with one or more sympathomimetic amines, such as ephedrine and phenylpropanolamine (PPA). Little is known about the behavioral pharmacology in humans of the combined effects of these drugs, including effects when individuals exceed the therapeutic dosage in an attempt to achieve amphetamine-like euphoria. These studies, which are in progress, are investigating the drugs both singly and in combination.

Another series of studies, in progress, is aimed at refining the drug self-administration paradigm presently used to enable more systematic evaluation of the reinforcing effects of opioids. This study of opioid self-admininistration will then be extended to evaluate the role of behavioral factors as modulators of the reinforcing effects of the drugs.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00306-07 CDM

PERIOD COVERED

October 1 1992 to September 30 1993

TITLE OF PROJECT

Pharmacokinetics and Pharmacodynamics of Opiate Analgesics

PRINCIPAL INVESTIGATOR

P.I.	EJ Cone	Chief	Clinical Pharmacology Branch
	WD Darwin	Chemist	Clinical Pharmacology Branch
	D Yousefnejad	Chemist	Clinical Pharmacology Branch
	A Jenkins	Staff Fellow	Clinical Pharmacology Branch
	W Wang	Visiting Fellow	Clinical Pharmacology Branch

COOPERATING UNITS

LAB/BRANCH

Clinical Pharmacology Branch

SECTION

Chemistry

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
0.8	0.3	0.5

CHECK APPROPRIATE BOXES

☒ (A) Human ☐ (b) Human Tissue ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

The pharmacokinetic and pharmacodynamic effects of single doses of parenterally administered opiates (heroin, morphine, hydromorphone, codeine, oxycodone, oxymorphone and sublingual buprenorphine) were studied. Concentrations of drug in blood and saliva levels were compared to pharmacologic effects. Additionally, the study was performed to determine if a metabolic marker for heroin abuse could be found in urine and other biological fluids.

The subjects were healthy males with a history of heroin abuse. Informed consent was obtained and all procedures were approved by the hospital Institutional Review Board. A total of three test doses (placebo and two active doses) were administered in random order. Test measures were made for 24 hours and biological fluids were collected for 7 days after each test. The biological fluids were analyzed for drug and metabolites by chromatographic and immunoassay techniques.

The significance of this study lies in the characterization of drug and metabolites appearance and disappearance over time and their relationship to drug-induced effects. Also, this continues our search for metabolite markers for heroin and other opiates in urine, saliva and other biological samples.

Goldberger, B. A., Darwin, W. D., Grant, T. M., Allen, A. C., Caplan, Y. H. and Cone, E. J. Measurement Of Heroin And Its Metabolites By Isotope-Dilution Electron-Impact Mass Spectrometry. Clin. Chem. 39: 670-675, 1993.

Cone, E.J., Holicky, B.A., Grant, T.M., Darwin, W.D. and Goldberger, B.A., Pharmacokinetics and Pharmacodynamics of Intranasal "Snorted" Heroin. J. Anal. Toxicol., In Press, 1993.

Walsh, S., Preston, K., Stitzer, M., Cone, E.J. and Bigelow, G., Buprenorphine and Methadone: Dose Ranging Studies in Human Substance Abusers. Clin. Pharmacol. Ther., In Press, 1993.

CHAPTERS:

Goldberger, B.A. and Cone, E.J. "Heroin" In Encyclopedia Of Analytical Science, In Press, 1993.
Cone, E.J. and Dickinson, S.L., "Efficacy Of Urinalysis In Monitoring Heroin And Cocaine Abuse Patterns-Implications, In Clinical Trials For Treatment Of Drug Dependence", NIDA Monograph, In Press, 1993.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00310-05 CDM

PERIOD COVERED

October 1 1992 to September 30 1993

TITLE OF PROJECT

Assessment of the Risk of Passive Inhalation of Drugs of Abuse

PRINCIPAL INVESTIGATOR

P.I.	EJ Cone	Chief	Clinical Pharmacology Branch
	WD Darwin	Chemist	Clinical Pharmacology Branch
	D Yousefnejad	Chemist	Clinical Pharmacology Branch

COOPERATING UNITS

LAB/BRANCH

Clinical Pharmacology Branch

SECTION

Chemistry

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER
0.7	0.1	0.6

CHECK APPROPRIATE BOXES

☒ (A) Human ☐ (b) Human Tissue ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

When drugs of abuse are smoked, volatile components and pyrolysis material escape into the atmosphere. Depending on the local environment, bystanders may be exposed to the drug by passive inhalation of the contaminated air.

Artificial methods have been developed to smoke drugs of abuse in a controlled environment and to measure drug air levels. These methods are then applied to the design of human clinical studies to assess the hazards of environmental exposure to drugs. Initially, free-base cocaine "crack" and methamphetamine "ice" will be evaluated.

Unknowing drug exposure could be dangerous to unsuspecting bystanders, particularly to small children. These studies will establish limits of exposure to volatile components of drugs under controlled conditions.

Gleason, C. , A., O'Brien, T., Jones, D. M., Jr., Cone, E. J., and Traystman, R. J. Fetal Cerebral Responses to Acute Maternal Cocaine Injection in Sheep. Amer. J. Physiol., In Press, 1992.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00312-05 NDAS

PERIOD COVERED

October 1 1992 to September 30 1993

TITLE OF PROJECT

Ligand-gated Ion Channels

PRINCIPAL INVESTIGATOR

P.I.	ED London	Chief	Neuroscience Branch
	RD Kusztos	Visiting Associate	Neuroscience Branch
	A Muhkin	Visiting Scientist	Neuroscience Branch
	K Hashimoto	Visiting Fellow	Neuroscience Branch

COOPERATING UNITS

LAB/BRANCH

Neuroscience Branch

SECTION

Neuroimaging and Drug Action

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
1.65	1.65	0

CHECK APPROPRIATE BOXES

☐ (A) Human ☐ (b) Human Tissue ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

@This project focuses on the molecular mechanisms that modulate the functions of the N-Methyl-D-aspartate preferring subtype of glutamate receptor (NMDA-R). NMDA-R is important because phencyclidine interacts with sites located inside the ion channel formed by this receptor, and neurotransmission mediated by this receptor has been implicated in opioid tolerance and dependence (see project report on the physiological effects of opioids). Discovery of the molecular mechanisms modulating NMDA-R function may lead to a better understanding of substance abuse and to the discovery of new treatments for substance abuse. Studies on the modulation of this receptor by polyamines reveal that the glutamate recognition site exists in high- and low-affinity states. The relative proportions of sites in these affinity states, assayed in vitro under conditions of low molarity buffer, in unperturbed tissue are 20% and 80%, respectively. Polyamines convert NMDA-Rs from the low affinity state to the high affinity state in a dose-dependent manner. This conversion can also be accomplished by incubating membranes in the presence of mono- and divalant cations. However, the potency of these cations is lower than that of polyamines. These studies suggest that polyamines may modulate the NMDA-R by more than one mechanism. At low temperature, radiolabeled ifenprodil (in the presence of GBR 12909 to mask sigma receptors; see project report on imaging sigma receptors) binds to polyamine sites on NMDA-Rs. Endogenous mechanisms regulating the function of the nicotinic acetylcholine receptor (nAChR) also are studied. Radiolabeled mecamylamine is used as a probe for the nAChR channel. At concentrations near those at which they occur in brain, polyamines exert an uncompetitive inhibition of binding of mecamylamine, suggesting that polyamines are endogenous modulators of nAChR.

Ritz MC, CR Mantione, and ED London: Spermine interacts with cocaine binding sites on dopamine transporters. Psychopharmacology., in press.

Hashimoto K and ED London: Specific binding sites for polyamines in brain. In: Neuropharmacology of Polyamines, CJ Carter, ed., Academic Press, London, in press.

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NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00314-04 MNS

PERIOD COVERED

October 1 1992 to September 30 1993

TITLE OF PROJECT

Human Dopaminergic Genes and Substance Abuse Vulnerability

PRINCIPAL INVESTIGATOR

P.I.	GR Uhl	Branch Chief	Molecular Neurobiology Branch
	A Persico	Visiting Fellow	Molecular Neurobiology Branch

COOPERATING UNITS

S Smith, Univ. of Wisconsin

LAB/BRANCH

Molecular Neurobiology Branch

SECTION

Molecular Neurobiology

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
11.05	0.3	0.75

CHECK APPROPRIATE BOXES

☒ (A) Human ☐ (b) Human Tissue ☐ (c) Neither

☐ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK

There are large individual differences among humans and animals in behavioral, physiological and toxicological responses to drugs of abuse. Individual differences in human behavioral responses to drugs appear to display substantial genetic influences, although these influences may be provided by several genes. Family studies suggest several severe limitations to pedigree-based linkage approaches in drug abuse, suggesting that association studies might be more fruitful. Use of allelic association approaches also mandated careful examination of ethnic differences in populations and linkage disequilibrium at specific loci that can confound these approaches.

Association studies with polymorphic markers at several different dopaminergic gene loci can test the hypothesis that interindividual differences in genes of dopaminergic neurotransmission could contribute to interindividual differences in vulnerability to substance abuse. During this fiscal year, this laboratory has continued to develop evidence that variants of the dopamine D2 receptor gene, marked by specific TaqI RFLP polymorphic markers, predispose to vulnerability to drug abuse. This work is accompanied by work documenting racial and ethnic differences in these marker frequencies, as well as striking and specific patterns of linkage disequilibrium across three markers at the D2 receptor gene locus. Interestingly, psychopathic substance abusers display gene marker frequencies no higher than those manifest by nonpsychopathic drug abusers.

Studies of RFLP or VNTR polymorphic markers at the dopamine transporter and synaptic vesicular monoamine transporter loci failed to reveal allelic association in a number of the same research subjects. However, the striking linkage disequilibrium found at the D2 receptor gene locus does not exist for at least several of the dopamine transporter locus markers, rendering them less effective reporters for possible allelic variants in these dopaminergic genes.

O'Hara BF, Smith SS, Bird G, Persico AM, Suarez B, Cutting GR, Uhl GR. Dopamine D2 Receptor RFLPs haplotypes and their association with substance use in black and caucasian research volunteers, Hum Hered 1993;43: 209-18.

Persico AM, O'Hara BF, Farmer S, Gysin R, Flanagan SD, Uhl GR. Dopamine D2 receptor gene Taq 1 'A' locus map including 'A4' variant: relevance for alcoholism and drug abuse, Drug Alcohol Depend 1993;31:229-34.

Persico AM, Vandenbergh DJ, Smith SS, Uhl GR. Dopamine transporter gene polymorphisms are not associated with polysubstance abuse, Biol Psychiatry 1993;in press.

Persico AM, Smith SS, Uhl GR. D2 receptor gene variants and substance abuse liability, Semin Neurosci 1993;in press.

Smith SS, Newman JP, Evans A, Pickens R, Wydeven J, Uhl GR, Newlin DB. Comorbid psychopathy is not associated with increased D2 dopamine receptor TaqI A or B gene marker frequencies in incarcerated substance abusers, Biol Psychol 1993; in press.

Uhl G, Blum K, Noble E, Smith S. Substance abuse vulnerability and D2 receptor genes, TINS 1993;16(3):83-8.

Uhl GR. Molecular and genetic studies of the targets of acute drug action, substrates for interindividual differences in vulnerability to substance abuse, and candidate mechanisms for addiction. In: Molecular approaches to drug abuse research: Rockville, MD: Dept. of Health and Human Services, National Institute on Drug Abuse Research
Monograph 1993;in press.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00327-05 MPS

PERIOD COVERED

October 1 1992 to September 30 1993

TITLE OF PROJECT

Endocrine Responses of Rats to Multiple Administration of Cocaine or Saline

PRINCIPAL INVESTIGATOR

P.I.	N Pilotte	Staff Fellow	Neuroscience Branch
	WM Mitchell	Lab Manager	Neuroscience Branch

COOPERATING UNITS

LAB/BRANCH

Neuroscience Branch

SECTION

Molecular Pharmacology

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
0.25	0.25	0

CHECK APPROPRIATE BOXES

☐ (A) Human ☐ (b) Human Tissue ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

Ongoing studies to determine if the repeated intravenous infusions of cocaine affect the regulation of the hypothalamo-pituitary-adrenal (HPA) axis in rats were completed. We found that the ability of the HPA axis to mount a normal response to the repeated administrations of the drug was intact. Thus, ACTH and corticosterone both increase initially after the first injection of cocaine. Corticosterone, with a longer half-life in plasma, then prevents the further CRH-mediated release of ACTH. In addition, the corticotrope responds normally to the release of arginine vasopressin from the posterior pituitary that is induced by blood volume depletion; and the corticosterone response occurred only in rats in which the anterior pituitary gland was present. Because repeated stimulation of the HPA axis by cocaine does not impair its response to the repeated stress that can be induced by the drug, it is likely that the immunosuppressive actions of cocaine are not mediated by the HPA system.

Studies of the long-term endocrine effects of the prenatal administration of cocaine were also continued. Prolactin is a hormone normally inhibited by hypothalamic dopamine. The basal prolactin levels in males from mothers treated with cocaine throughout pregnancy, were 60% higher than in controls. Growth hormone, which is regulated primarily by peptidergic factors, was unaffected. Decreasing the dose of cocaine or limiting its administration to gestational days 8-22 resulted in normal basal levels of prolactin in the adult rats. These results suggest that prenatal exposure to a high dose of cocaine early in pregnancy can significantly affect the regulation of prolactin in adult rats and that there may be a critical period in early gestation in which cocaine can influence the development of at least one dopaminergic system such that changes in the regulation of prolactin persist into adulthood. We are currently using autoradiographic methods to determine if the prenatal treatments affected the binding of the dopamine transporter in the forebrain of these rats.

Pilotte, NS and Kornak, EP. (1993) Adrenocorticotropin and corticosterone in male rats during multiple repeated intravenous administrations of cocaine. Submitted to Neuroendocrinology.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00328-06 CDM

PERIOD COVERED

October 1 1992 to September 30 1993

TITLE OF PROJECT

Pharmacokinetics and Pharmacodynamics of Drugs of Abuse in Hair

PRINCIPAL INVESTIGATOR

P.I.	EJ Cone	Chief	Clinical Pharmacology Branch
	WD Darwin	Chemist	Clinical Pharmacology Branch
	D Yousefnejad	Chemist	Clinical Pharmacology Branch
	W Wang	Visiting Scientists	Clinical Pharmacology Branch

COOPERATING UNITS

LAB/BRANCH

Clinical Pharmacology Branch

SECTION

Chemistry

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
1	0.9	0.1

CHECK APPROPRIATE BOXES

☒ (A) Human ☐ (b) Human Tissue ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

Drug residues have been detected in human hair specimens by a variety of analytical techniques. These reports have generated substantial interest in using hair as a historical record of drug usage. Current studies are designed to determine the presence and time course of drugs of abuse in human hair.

Healthy male volunteers with a history of chemical substance abuse participated in the study. Informed consent was obtained and all procedures were approved by the hospital Institutional Review Board. Subjects resided on the clinical ward of the ARC. Head and facial hair specimens were obtained prior to and after administration of drugs of abuse. Blood, saliva and urine specimens also were obtained. Analyses of tissue and biofluids for drug was performed by radioimmunoassay and gas chromatography/mass spectrometry.

These studies provide the scientific basis for determination of the usefulness of hair as a "historical record" for substance abuse.

PUBLICATIONS

Cone, E. J., Darwin, W. D. and Wang, W., The Occurrence Of Cocaine, Heroin And Metabolites In Hair Of Drug Abusers. Forensic Sci. Int., In Press, 1993.

CHAPTER:

Cone, E.J., "Hair Analysis as a Drug Use, " In Clayton, R.R., Johnson, C.E., Kuhar, M.J., Et Al. (Eds.) The Encyclopedia Of Drugs and Alcohol., Macmillan Publishing Company, New York, In Press, 1993


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